TREATMENT OF POST-ORTHODONTIC WHITE SPOT LESIONS USING BIOACTIVE GLASS: A RANDOMIZED CONTROLLED TRIAL WITH 12-MONTHS FOLLOW-UP

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ABSTRACT

INTRODUCTION: To evaluate the effect of bioactive glass 45S5 in comparison to casein phosphopeptide amorphous calcium phosphate (CPP-ACP) for the treatment of post-orthodontic white spot lesions (WSLs).

METHODS: Sixty patients with acquired post-orthodontic WSLs (score 2 ICDAS II) were recruited and randomly allocated to a double blind three-arm randomized controlled trial (n=20). Test group I (Bio-B45S5), test group II (Nov-B45S5), and the control group (CPP-ACP) received BiominF, Novamin, and Recaldent pastes respectively. Products were applied daily in-office during week 1, in addition to once per day home application for four weeks starting day 1. Standardized intraoral photographs and laser fluorescence DIAGNOdent were used for assessment at baseline (T0), 1 week (T1), 1 month (T2), 3,6,9, and 12 months (T3, T4, T5, T6 respectively). **RESULTS:** At T6, a statistically significant (p < 0.001) WSL regression was shown in all groups compared to baseline. Additionally, a highly significant reduction in WSL proportionality was observed in Bio-B45S5 group compared to the control group (p < 0.001). The mean area of the lesions decreased by 67% in the Bio-B45S5 group, 37% in the Nov-B45S5group, and 39% in the CPP-ACP group (p=0.001). DIAGNOdent findings were largely reflected by the clinical scores (Mean scores at baseline/T6 for groups I, II, and III respectively; 16.98/2.68, 16.93/7.11, 28.38/20.50).

Conclusions:

Compared to Novamin and CPP-ACP, BiominF resulted in greater esthetic improvements as well as a significant reduction in fluorescence intensity which indicates potential lesion remineralization.

KEYWORDS: BiominF, Novamin, CPP-ACP, Remineralization, DIAGNOdent laser fluorescence. **RUNNING TITLE:** Bioactive glass in white spot lesions treatment.

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INTRODUCTION

Newly developed ultraconservative operative procedures and refraining from traditional surgical techniques accounted for a greater preservation of dental tooth structure . Minimal intervention dentistry (MID) involves the use of preventive as well as remineralizing measures in the management of early enamel white spot lesions while withholding from unnecessary dental tissue destruction (2).

White spot lesions (WSLs) are frequently observed following fixed orthodontic treatment. The resulting esthetic impairment can be explained by the physicochemical processes occurring around orthodontic brackets. Plaque accumulation and bacterial acid attack leads to subsurface mineral loss thereby, giving enamel a porous internal structure. WSLs appear as opaque chalky white segments persistent even after treatment cessation (3, 4). A partially mineralized surface is naturally restored via re-

incorporation of salivary calcium and phosphate though the body of the defect remains porous in nature (3, 5). Being the earliest clinical manifestation of caries, the enamel white spot lesion is considered reversible at early stages up to a point of surface cavitation. Consequently, non-invasive remineralization techniques have been developed (6, 7). Remineralization therapies include; topical fluorides in various forms, Milk product-based complexes such as Recaldent, and, bioactive glass 45S5 as a new modality. Although topical fluorides are well known for arresting caries progression and, are considered standard treatment for carious lesions. the Unfortunately, "arresting" WSLs results in permanent esthetic impairment through persistent lesions. Studies have demonstrated that fluoride application for WSL treatment can induce a hyper-mineralized surface, thereby preventing ion diffusion into the body of the lesion. Based on these conclusions,

Fluoride varnishes and high-concentration Fluoride gels have been excluded from this trial (8-13).

Another common treatment option which has been heavily studied for the past 20 years is casein phosphopeptide amorphous calcium phosphate (CPP-ACP). Systematic reviews and meta-analyses by Ma et al. and, Imani et al. have recently established CPP-ACP as an effective remineralizing agent suitable for WSL treatment (14, 15). CPP-ACP acts by maintaining a supersaturated level of essential ions such as calcium and phosphate within the biofilm promoting mineral deposition. In comparison with fluorides, CPP-ACP products were proven effective as preventive and therapeutic agents while effects of fluorides in reversing WSLs remained unclear (16).

Bioactive glass 45S5 (BAG), a degradable highly reactive glass developed in 1969, have been used extensively as a bone graft as it is capable of bonding to host tissues and inducing bone formation. BAG employed Recently. was in dental remineralization therapies with promising results. BAG acts as a source of high amounts of calcium and phosphorus rapidly dissolving in aqueous solutions. Moreover, BAG forms an intimate bond with the tooth structure in less than two hours and induces apatite formation (17, 18). Previous in vitro studies by zhang et al., Bakry et al. and, Milly et al. presented promising results for two novel types of bioactive glass 45S5; BiominF (Bio-B45S5) and Novamin (Nov-B45S5). Therefore, further clinical investigations are currently required (5, 19-21).

In light of the previous literature, this study aims to clinically evaluate the effect of two types of bioactive glass 45S5 namely; BiominF and, Novamin in comparison to CPP-ACP for WSL treatment. Computer aided analysis of digital intra-oral photographs in addition to DIAGNOdent laser florescence were used for assessment. The null hypothesis states; no significant difference regarding WSL remineralization can be detected between the three groups.

MATERIALS AND METHODS

Registration

This trial was registered on ClinicalTrials.gov (Identifier: NCT04401280).

Ethical issue

Ethical approval was obtained following the guidelines of the Institutional Review Boards (IRB) by the Ethics Committee of the Faculty of Dentistry, Alexandria University, Egypt. (IRB NO 00010556-IORG 0008839). All patients signed an informed consent sheet upon participation in this study.

Trial design

A randomized, controlled, assessor, statistician and patient blinded single center trial with 3 parallel groups. Randomization with a 1:1:1 allocation ratio was performed. Throughout this trial, the Consolidated Standards of Reporting Trials (CONSORT) guidelines were performed (Fig. 1) (22).



Fig. 1 CONSORT flow diagram showing patient flow during the trial.

Patient screening

60 patients (aged 14-26 years) with post-orthodontic WSLs were recruited from the outpatient clinics of the school of dentistry of the local university. 1-3 lesions per patient were considered and, an average was calculated for each patient during assessment (82 teeth in total). Lesions found strictly on the labial aspect of anterior/premolar teeth were included and were limited to code 2 International Caries Detection and Assessment System II (ICDAS-II). Code 2 is defined as a distinctly visible change in enamel including changes in opacity or discoloration which is detectable without drying (23). Exclusion criteria consisted of; teeth with cavities or restoration, recent fluoride treatments, enamel defects (e.g. hypoplasia, amelogenesis imperfecta, etc.), bracket debonding more than 6 months and, patients with allergies to milk proteins.

Interventions

In total, ten visits were scheduled. The study lasted from June 2020 (initial recruitment) to September 2021 (12 month follow-up) (24, 25). After initial assessment, the teeth were examined carefully for residual bonding agents, cleaned and polished using fluoride-free slurry (pumice). For Bio-B45S5 and Nov-B45S5 groups, a remineralizing paste was prepared during in office sessions according to Bakry et al. technique (19). One tenth of a gram of powder (BiominF or Novamin respectively) was carefully mixed on a glass slab for sixty seconds with 2 or more drops of 50 wt% phosphoric acid until a paste consistency was obtained. The fresh mix was immediately applied by the operator in a standardized manner. Soft tissues were retracted using a dental lip and cheek retractor and teeth were dried for five seconds using oil-free compressed air. A microbrush was used for application without agitation and the teeth were left undisturbed for thirty minutes. Finally, a layer of bonding agent was gently applied

on the surface (Prime & Bond universal adhesive, Dentsply Maillefer, Ballaigues, Switzerland), and light-cured using LED (WoodpeckerTM LED Curing light, China 900 mW/cm2 output) for twenty seconds.

Subjects were instructed to refrain from eating or drinking for one hour following the procedure and to remove the applied materials at night to allow for home application. On the following day, residual bonding agent was removed carefully in-office and, the procedure was repeated. Overall, seven consecutive visits were scheduled for in-office application (Fig. 2).



Fig. 2 Daily in-office application of Nov-B45S5 paste on tooth no. 34 followed by bonding and curing.

Starting Day 1 (T0), dental hygiene products corresponding to each group were supplied for homeuse; Group I received BiominF toothpaste (Biomin Technologies Ltd., Mile End, London, UK) while group II received Sensodyne repair and protect (GlaxoSmithKline plc., England). A soft hardness toothbrush (Oral-B Indicator 35 soft) was also provided to control for brushing abrasion (Procter & Gamble, USA). Patients were instructed to apply the products daily (at night) for thirty days starting day 1 (First in-office session). Instructions recommended brushing the paste as usual onto all teeth for two minutes using the supplied toothbrush then spitting out the excess foam without rinsing, eating and drinking was to be avoided until the next morning. All patients were provided with written instructions, in addition to a one month chart as a reminder for daily use. Similarly, for the control group, Recaldent paste was applied daily for a week during in office sessions, followed up by daily home-use according to the manufacturer's instructions for a period of one month.

All materials provided were enclosed into identical label free containers of equal weight. The materials had similar consistencies and were colorless/ odorless. The weight of each container was recorded on every follow-up visit to assess patient compliance. During months 2-12, standard oral hygiene care using fluoride-free toothpastes was performed.

Standardized Intraoral Photographs

Measurements were obtained before treatment (T0) and at a 1 week (T1), 1 month (T2), 3 month (T3), 6 month (T4), 9 and 12 month intervals (T5.T6). Photographs were shot in standard lighting conditions using a Nikon D3200 digital single lens reflex (DSLR) camera equipped with a Sigma 105mm f/2.8 EX DG OS HSM macro lens. In order to minimize reflections, Godox TT520ii external flash and a ring softbox were used. The camera was secured in a fixed position at a fixed distance with a 1:1 magnification ratio. By seating the patients in an upright position, shots were taken perpendicular to the labial surface of each tooth. Prior to image analysis each photograph was cropped to show one tooth in the field and, adjusted for brightness/ contrast (if needed) using Photoshop (version Cs 4.0, Adobe systems Inc, USA). The photos were then saved as TIFF data files, and further processed using Imagej 1.53a, NIH software. A clear selection of the lesion and the entire labial surface was done using the free hand selection tool. Selection borders were manually adjusted on high magnification for better accuracy (Fig. 3). Using the measuring tool, areas of the lesion and of the labial surface were automatically calculated in pixels.



Fig. 3 imagej processing steps in tooth no.44: a. untouched image, b. marking the lesion outline using free-hand selection tool. c. marking the entire labial surface and adjustment of selection points.

Study Parameters

Primary outcome measures:

WSL proportionality (WSL %) defined as the ratio of the lesion area to the entire labial surface area of the tooth: WSL% = $\frac{Area \ of \ WSL}{Area \ of \ the \ labial \ surface}$ X100. Dimensional change (Lesion size percent change) over a period of 12 months (Δ WSL%) was calculated for all samples. Δ WSL% = $\frac{WSL\%(T6) - WSL\%(T0)}{WSL\%(T0)} \times 100$ (26, 27). After 2 weeks, a new computer random order was generated and the images were reanalyzed

by a single calibrated examiner.

Secondary outcome measures:

The fluorescence intensity of each lesion was assessed using DIAGNOdent Classic laser florescence (KaVo Dental, Biberach, Germany). The device tip was positioned in the center of the lesion after drying for five seconds with a gentle air stream to avoid dehydration, and exploratory motions encompassing the entire lesion surface were conducted until the highest value (peak) was recorded. Each surface was scanned two times for confirmation and, the device was calibrated before each use. Measurements were recorded at baseline, 1 week, 1, 3, 6, 9 and 12 months.

Sample size calculations

Sample size was estimated assuming 5% alpha error and 80% study power. Estimates of subsurface remineralization potential of the agents were based on findings of previous studies (19, 20). Based on comparison of means, using one-way ANOVA test, the minimum sample size was calculated for detecting a moderate effect size of 0.53, to be 18 per group, increased to 20 to make up for cases lost to follow up. The total sample size required to detect the effect of different agents on remineralization of white spot lesions = number of groups × number per group= $20 \times 3 = 60$ (28).

Randomization, blinding and allocation concealment

The participants were assigned randomly to one of three groups with a 1:1:1 allocation ratio. Groups include: test group I (Bio-B45S5), test group II (Nov-B45S5) and control group (CPP-ACP). The sealed envelope system was used for blinding and randomization. A computer-generated table of random numbers was used. An impartial person who was not involved in the study created cards with the details of each group and placed them in sealed opaque envelopes. The envelope was opened by this independent person and the allocation assignment was revealed after the subject was scanned to meet the inclusion criteria and baseline assessments were recorded by the lead investigator. All clinical procedures were conducted by a single trained examiner. Treatment allocation was concealed from the data assessor, patients, and statistician.

Statistical analysis

All variables were checked for normality using descriptive statistics, graphs, and normality tests. For quantitative data, mean, standard deviation (SD), median, and interquartile range were computed, whereas for qualitative variables, frequencies and percentages were calculated. Lesion size percent change (Δ WSL %) was calculated using the formula: $\frac{Value \ at \ T6-Value \ at \ T0}{X100} \times 100.$ One-way ANOVA was Value at T0 used to compare quantitative variables across the three research groups for normally distributed variables (age), and Kruskal Wallis test was used for non-normally distributed variables (number of affected teeth, time since appliance removal, lesion size, and DIAGNOdent readings). Friedman test was used to compare different time points within each group. Bonferroni adjusted significance levels were used in post-hoc multiple pairwise comparisons. When indicated, chi-square tests with Monte Carlo correction were used to compare qualitative variables between the three research groups. All groups were analyzed using intention to treat analysis via IBM SPSS for Windows (Version 23.0).

RESULTS

Patients flow

The study included 60 patients (39 females, 21 males; with a mean age of 21.8 years) having 82 WSLs (44 maxillary, 38 mandibular). A maximum of 3 lesions were considered and an average score was calculated for every patient during the analysis. A total of 55 participants (37 females, 18 males; with a mean age of 21.8 years) having 76 WSLs (40 maxillary, 36 mandibular) were available at T6. Of the included subjects, 5 were lost during the trial, and 5 missed only one appointment at (T1, T2, T4, T5, T6). During the course of the trial, no serious adverse events were reported. Within the three groups, common cold episodes with rhinitis/cough were observed. None of which, however, appears to be relevant to the study products.

Baseline findings

The three groups were comparable in terms of ethnicity, gender and several other baseline characteristics except for age (Table 1). No significant general health conditions were detected at baseline.

Primary outcome:

Change in WSL proportionality ($\Delta WSL\%$)

Table 2 shows the average change in lesion size percentage (Δ WSL%) for all groups over a 12-month follow-up period. Average white spot lesion proportionality (WSL%) values at baseline for group I (Bio-B45S5), group II (Nov-B45S5), and group III (CPP-ACP) were 18.45 ± 15.24, 24.75 ± 10.78, and 26.65 ± 12.05, respectively. Over the course of the trial, all three remineralizing agents resulted in a significant reduction (P < 0.001) in the mean value of (WSL%). Values at T6 for groups I, II, and III respectively were 5.03 ± 3.58 , 15.59 ± 8.20 , and 16.27 ± 9.33 . Compared to the control group, Bio-B45S5 group showed a significant statistical difference at T6 (p 0.001), whereas the Nov-B45S5 group showed no significant statistical difference.

 Table 1 Baseline characteristics of the three study groups:

		Biomin	Novami	CPP-	P value
		F		ACP	
		(n= 20)	(n= 20)	(n= 20)	
Age (Mean \pm SD) ¹		$19.90 \pm$	$21.80~\pm$	23.75 ±	<0.001*
		2.83 a	2.46 b	1.68 c	
Gender: n	Male	8	6 (30%)	7	0.80
(%) ²		(40%)		(35%)	
	Female	12	14	13	
		(60%)	(70%)	(65%)	
Ethnic	Caucasian/Arab	18	19	20	P _{MC} :
origin: n		(90%)	(95%)	(100%)	0.77
(%) ²	African/Black	2	1 (5%)	0	
		(10%)		(0%)	
Oral	Very good	4	7 (35%)	5	P _{MC} :
hygiene		(20%)		(25%)	0.06
level: n	Good	8	8 (40%)	8	
$(\%)^2$		(40%)		(40%)	
	Fair	6	5 (25%)	0	
		(30%)		(0%)	
	Poor	2	0 (0%)	5	
		(10%)		(25%)	
Number of affected teeth		1.40 ±	$1.50 \pm$	$1.20 \pm$	0.45
$(Mean \pm SD)^3$		0.68	0.76	0.41	
Weeks since appliance		$7.17 \pm$	$7.32 \pm$	$9.34 \pm$	0.90
removal (Mean \pm SD) ³		7.86	8.42	6.89	

¹ one-way ANOVA, ² chi-square, ³ Kruskal Wallis tests were used

P_{MC}: Monte Carlo corrected p value

*statistically significant at p value < 0.05

a,b,c: different letters denote statistically significant differences between groups using Bonferroni adjusted significance levels

Secondary outcome:

Table 3 summarizes the changes in DIAGNOdent scores. The mean DIAGNOdent score at baseline was comparable among the three groups (p = 0.07). The average scores in group I decreased from 16.98 \pm 14.34 at baseline to 2.68 \pm 4.40 at T6. Similarly, DIAGNOdent scores decreased in groups II and III during the study period, but to a lesser extent; group II decreased from 16.93 \pm 17.39 to 7.11 \pm 8.09 by the end of the study while group III only decreased from 28.38 \pm 20.80 to 20.50 \pm 22.83. At T6, Bio-B45S5 group showed a significant statistical difference in comparison with the control group (P <0.001).

Table 2 Change in white spot lesion proportionality $(\Delta WSL\%)$ in the three study groups at different time points:

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		BiominF	Novamin	СРР-	KWT
		(n= 20)	(n= 20)	ACP	P value
				(n= 20)	
T0	Mean ±	$18.45~\pm$	$24.75~\pm$	$26.65 \pm$	0.03*
	SD	15.24 a	10.78 a,b	12.05 b	
	Median	13.18	25.93	28.85	
	(IQR)	(9.73,	(14.15,	(15.88,	
		23.13)	32.32)	34.13)	
T1	Mean ±	$14.04~\pm$	$19.71 \pm$	$20.16~\pm$	0.08
	SD	12.64	10.71	10.16	
	Median	10.14	18.55	20.95	
	(IQR)	(7.68,	(10.20,	(9.25,	
		15.53)	27.63)	28.16)	
T2	Mean ±	11.27 ±	$13.19 \pm$	$18.34 \pm$	0.02*
	SD	12.20 a	8.03 a,b	9.96 b	
	Median	8.15	10.57	18.65	
	(IQR)	(3.85,	(8.70,	(8.75,	
		11.80)	17.92)	28.44)	
Т3	Mean ±	$8.30 \pm$	17.13 ±	17.87 ±	<0.001*
	SD	8.16 a	8.94 b	9.69 b	
	Median	7.08	16.48	18.65	
	(IQR)	(2.83,	(9.88,	(8.46,	
		8.85)	21.71)	26.39)	
T4	Mean ±	$5.68 \pm$	$17.03 \pm$	$17.36 \pm$	<0.001*
	SD	3.79 a	8.90 b	9.58 b	
	Median	5.16	16.82	17.00	
	(IQR)	(2.35,	(9.52,	(8.39,	
		7.55)	20.59)	25.54)	
Т5	Mean ±	$5.35 \pm$	$16.19 \pm$	$16.71 \pm$	<0.001*
	SD	3.74 a	8.63 b	9.24 b	
	Median	4.80	15.15	16.50	
	(IQR)	(2.10,	(9.70,	(8.26,	
		7.10)	20.77)	24.80)	
T6	Mean ±	$5.03 \pm$	$15.59 \pm$	$16.27 \pm$	<0.001*
	SD	3.58 a	8.20 b	9.33 b	
	Median	4.53	13.90	16.00	
	(IQR)	(2.10,	(9.77,	(7.84,	
		6.89) a	20.57)	24.40)	
Percent	Mean ±	-67.07 \pm	$-37.64~\pm$	-39.18	<0.001*
change	SD	20.12 a	13.79 b	± 21.11	
				b	
	Median	-72.29	-36.56	37.05	
	(IQR)	(-84.11,	(-49.85, -	(-55.76,	
		-52.97)	29.75)	-25.69)	
Friedma	an test p	<0.001*	<0.001*	<0.001*	
val	lue				

KWT: Kruskal Wallis test was used

*statistically significant at p value < 0.05

a,b: different letters denote statistically significant differences between groups using Bonferroni adjusted significance levels

Table 3 DIAGNOdent readings in the three study
groups at different time points:

		BiominF (n= 20)	Novamin (n= 20)	CPP-ACP (n= 20)	KWT P value
TO	Mean ± SD	16.98 ± 14.34	16.93 ± 17.39	28.38 ± 20.80	0.07
	Median (IQR)	13.83 (5.75, 21.25)	11.75 (4.00, 26.13)	24.00 (35.63, 15.38)	
T1	Mean ± SD	$9.87\pm9.79~a$	13.34 ± 9.86 a,b	22.08 ± 22.16 b	0.048*
	Median (IQR)	8.17 (3.00, 14.00)	10.00 (6.00, 19.50)	18.00 (7.50, 25.75)	
T2	Mean ± SD	$8.09 \pm 9.03 \ a$	$6.08\pm7.80~a$	26.70 ± 21.80 b	<0.001*
	Median (IQR)	5.75 (1.25, 12.75)	1.50 (0.00, 11.50)	26.50 (16.00, 33.00)	
T3	Mean ± SD	$3.86\pm5.43~a$	$7.86 \pm 9.19~a$	22.43 ± 22.97 b	0.001*
	Median (IQR)	0.75 (0.00, 7.25)	4.83 (0.25, 14.75)	16.00 (7.25, 30.00)	
T4	Mean ± SD	$3.57 \pm 4.88 \ a$	7.90 ± 8.20 a,b	22.07 ± 23.12 b	<0.001*
	Median (IQR)	1.00 (0.00, 6.25)	5.50 (2.00, 13.75)	15.25 (6.25, 30.50)	
Т5	Mean ± SD	3.11 ± 4.51 a	7.39 ± 7.72 a,b	21.05 ± 22.50 b	<0.001*
	Median (IQR)	0.33 (0.00, 5.75)	6.00 (0.50, 12.00)	14.00 (5.12, 29.00)	
T6	Mean ± SD	$2.68 \pm 4.40 \ a$	7.11 ± 8.09 a,b	20.50 ± 22.83 b	0.001*
	Median (IQR)	0.00 (0.00, 4.75)	4.00 (0.12, 12.00)	13.00 (5.00, 29.25)	
Percent change ¹	Mean ± SD	-86.62 ± 20.43 a	-42.48 ± 57.60 b	-39.20 ± 40.29 b	<0.001*
	Median (IQR)	-100 (-100, - 73.20)	-58.06 (- 88.00, 0.00)	-37.80 (- 57.53, - 13.45)	
Fried	man test p	<0.001*	<0.001*	<0.001*	

KWT: Kruskal Wallis test was used

*statistically significant at p value < 0.05 **a,b:** different letters denote statistically significant differences between groups using Bonferroni adjusted significance levels

While Bio-B45S5 group showed a consistent decline over the course of the trial, Nov-B45S5 group showed a significant increase between the 1 month and 3 months (T2, T3) follow up points for both digital analysis and DIAGNOdent scores. CPP-ACP group also should a consistent decline in WSL% however, DIAGNOdent readings increased between 1 week (T1) and 1 month (T2) follow-up points (shown in Fig. 4,5).



Fig. 4 Mean lesion size at different time points for the three study groups



Fig. 5 Mean DIAGNOdent scores at different time points for the three study groups

DISCUSSION

WSLs remain an ongoing challenge for clinicians. Though various preventive and therapeutic treatments have been introduced, WSL prevalence among orthodontic patients remains significantly high (29). Upon debonding, natural remineralization occurs through salivary ions. This process takes place to a variable extent and rarely reaches the full depth of the lesion. As a result, unsightly white patches may remain visible up to 12 years (30, 31). Previous research showed the potential of bioactive glass to be successfully employed in WSL remineralization therapies however, an ideal mode and duration of application is yet to be determined (5, 21, 32, 33). A few recent in-vitro studies by Bakry et al. recommended the use of bioactive glass containing pastes (BiominF[®] / Novamin[®] powder mixed with 50% phosphoric acid, covered with a layer of bonding agent) to arrest and reverse WSLs and showed promising results (19, 20). Therefore, this current study was conducted to clinically evaluate the remineralization potential of bioactive glasses type 4585.

For an intervention period of 1 month, 2 novel bioactive glasses namely BiominF and Novamin were used in comparison with CPP-ACP control paste to determine the remineralization effects on postorthodontic WSLs. The data presented was collected after a 12-month follow-up period.

The study results showed a significantly higher chance of regression for lesions within the Bio-B45S5 group as compared to Nov-B45S5 or CPP-ACP. Therefore, the null hypothesis was rejected.

Lesions in Bio-B45S5 group declined in size proportionality by 67% during 12 months, while those in Nov-B45S5 /CPP-ACP groups decreased by 37% and 39% respectively as was confirmed by digital image analysis and laser fluorescence assessment methods.

The percent reduction rate shown in this study (min: 32%/6 months – max: 62%/6 months) surpasses the natural slow rate of regression as reported by Willmot

D (50% decrease after 6 months with no intervention) and by Mattousch et al. who concluded that complete healing occurred in merely ten cases out of 370 after 2 years of follow up. Moreover, He et al. reported a complete lack of recovery in some cases and a restricted self-healing ability in others (8, 34, 35).

During this trial, the majority of WSL improvements occurred within the first three months in correspondence to materials application while the follow up period between 6 and 12 months was rather stagnant. This observation highlights the importance of rapid post-orthodontic intervention in such cases for more favorable outcomes.

Laser fluorescence evaluates structural changes within carious/demineralized lesions. Defective dental tissues contain more water and organic content than sound highly mineralized tissues. When subjected to Laser beams, the lesion acts as a highly scattering material and the path of light photons within the defect can be evaluated and quantified (36). For accurate assessment, digital image analysis was combined with laser fluorescence to evaluate both esthetic and structural aspects of WSLs as recommended by a recent systematic review (37). Another review by Lopatiene et al. Confirmed the validity of digital intra-oral photography as one of the most popular and well accepted methods for WSL assessment (38).

Bioactive glass 45S5 presents a breakthrough in WSL remineralization. When exposed to dental tissues, BAG rapidly forms strong chemical bonds that prolong the interaction period and facilitate ion diffusion into the lesion. Contrastingly, the amorphous nature of CPP-ACP hinders material retention for extended periods resulting in a decreased remineralization effect (39). In-vitro studies showed a larger more compact deposit when using BAG compared to smaller, loosely packed ACP plugs which supports the findings of this trial (40).

Despite the fact that BiominF and Novamin are both 45S5 BAGs, BiominF has a distinct mode of action. As previously mentioned, high concentrations of fluoride shock the enamel surface and prevent further penetration however, BiominF releases low levels of flouride along with high levels of calcium and phosphorus which enable the material to diffuse beneath the surface allowing for subsurface mineral deposition (8, 19). In addition, fluoride incorporation promotes the formation of highly stable fluorapatite crystals and prevents further deterioration of the lesion. In contrast, Novamin lacks fluoride in its composition, and forms Hydroxyapatite rather than fluorapatite crystals which may explain the consistency of Bio-B45S5 lesion improvements throughout the study and the relapse pattern of Nov-B45S5 after treatment cessation (Fig. 6) (41).



Fig. 6 Digital intra-oral photographs obtained from a 22-year-old female in Bio-B45S5 group (a-g) and a 19-year-old female in Nov-B45S5 group (h-n) at T0 (Baseline), T1 (1 week), T2 (1 month), T3 (3 months), T4 (6 months), T5 (9 months), and T6 (12 months). Bio-B45S5 showed a remarkable decrease in lesion size between T0-T6, while Nov-B45S5 showed improvement up to 1 month only followed by a relapse at T3, and a limited decrease between T4-T6.

Limitations

Patient compliance can hardly be controlled though efforts were made to limit the effects of this confounding factor such as constantly weighing the provided packages at each follow-up visit and combining self-administered home application with standardized in-office applications.

Conclusion

Bioactive glass 45S5 is a promising new material in WSL remineralization therapies. BiominF specifically is capable of consistently decreasing caries levels of non-cavitated White spot lesions while improving esthetics.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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REFERENCES

- Frencken J, Van Amerogen E, Phantumvanit P, Songpaisan Y, Pilot T. Manual for the Atraumatic Restaurative Treatment approach to control dental caries. Dental Health International Nederlant ISBN90-803296-1-4. 1997.
- Banerjee A. Minimal intervention dentistry: part
 Minimally invasive operative caries management: rationale and techniques. British dental journal. 2013;214:107-11.
- 3. Abdullah Z, John J. Minimally invasive treatment of white spot lesions-A systematic review. Oral Health Prev Dent. 2016;14:197-205.
- 4. Daculsi G, LeGeros R, Jean A, Kerebel B. Possible physico-chemical processes in human dentin caries. J Dent Res. 1987;66:1356-9.
- Zhang J, Lynch RJ, Watson TF, Banerjee A. Chitosan-bioglass complexes promote subsurface remineralisation of incipient human carious enamel lesions. Journal of Dentistry. 2019;84:67-75.
- 6. Selwitz RH, Ismail AI, Pitts NB. Dental caries. The Lancet. 2007;369:51-9.
- 7. González-Cabezas C, Fernández C. Recent advances in remineralization therapies for caries lesions. Adv Dent Res. 2018;29:55-9.
- 8. Willmot D, editor White spot lesions after orthodontic treatment. Semin Orthod; 2008: Elsevier.
- Bailey D, Adams G, Tsao C, Hyslop A, Escobar K, Manton D, et al. Regression of postorthodontic lesions by a remineralizing cream. J Dent Res. 2009;88:1148-53.
- 10. Retief D, Bradley E, Holbrook M, Switzer P. Enamel fluoride uptake, distribution and retention from topical fluoride agents. Caries research. 1983;17:44-51.
- Øgaard B, Rølla G, Arends J. Orthodontic appliances and enamel demineralization: Part 1. Lesion development. American Journal of Orthodontics and Dentofacial Orthopedics. 1988;94:68-73.
- 12. García-Godoy F, Hicks MJ. Maintaining the integrity of the enamel surface: the role of dental biofilm, saliva and preventive agents in enamel demineralization and remineralization. J Am Dent Assoc. 2008;139:25S-34S.
- Shen P, McKeever A, Walker GD, Yuan Y, Reynolds C, Fernando JR, et al. Remineralization and fluoride uptake of white spot lesions under dental varnishes. Australian Dental Journal. 2020.
- 14. Ma X, Lin X, Zhong T, Xie F. Evaluation of the efficacy of casein phosphopeptide-amorphous calcium phosphate on remineralization of white spot lesions in vitro and clinical research: a systematic review and meta-analysis. BMC Oral Health. 2019;19:1-11.
- 15. Imani MM, Safaei M, Afnaniesfandabad A, Moradpoor H, Sadeghi M, Golshah A, et al.

Efficacy of CPP-ACP and CPP-ACPF for prevention and remineralization of white spot lesions in orthodontic patients: a systematic review of randomized controlled clinical trials. Acta Informatica Medica. 2019;27:199.

- 16. Bakdach WMM, Hadad R. Effectiveness of different adjunctive interventions in the management of orthodontically induced white spot lesions: A systematic review of systematic reviews and meta-analyses. Dental and medical problems. 2020.
- 17. Jones JR. Review of bioactive glass: from Hench to hybrids. Acta biomaterialia. 2013;9:4457-86.
- 18. Narayana SS, Deepa VK, Ahamed S, Sathish ES, Meyappan R, Kumar KS. Remineralization efficiency of bioactive glass on artificially induced carious lesion an in-vitro study. Journal of indian society of pedodontics and preventive dentistry. 2014;32:19.
- 19. Bakry AS, Abbassy MA, Alharkan HF, Basuhail S, Al-Ghamdi K, Hill R. A novel fluoride containing bioactive glass paste is capable of remineralizing early caries lesions. Materials. 2018;11:1636.
- 20. Bakry A, Takahashi H, Otsuki M, Tagami J. Evaluation of new treatment for incipient enamel demineralization using 45S5 bioglass. Dental Materials. 2014;30:314-20.
- 21. Milly H, Festy F, Watson TF, Thompson I, Banerjee A. Enamel white spot lesions can remineralise using bio-active glass and polyacrylic acid-modified bio-active glass powders. Journal of dentistry. 2014;42:158-66.
- 22. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC medicine. 2010;8:18.
- Dikmen B. Icdas II criteria (international caries detection and assessment system). Journal of Istanbul University Faculty of Dentistry. 2015;49:63.
- 24. Bröchner A, Christensen C, Kristensen B, Tranæus S, Karlsson L, Sonnesen L, et al. Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilised amorphous calcium phosphate. Clinical oral investigations. 2011;15:369-73.
- 25. Mendes AC, Restrepo M, Bussaneli D, Zuanon AC. Use of casein amorphous calcium phosphate (CPP-ACP) on white-spot lesions: Randomised clinical trial. Oral Health Prev Dent. 2018;16:27-31.
- 26. Gu X, Yang L, Yang D, Gao Y, Duan X, Zhu X, et al. Esthetic improvements of postorthodontic white-spot lesions treated with resin infiltration and microabrasion: A split-mouth, randomized clinical trial. The Angle Orthodontist. 2019;89:372-7.

- 27. Willmot D. White lesions after orthodontic treatment: does low fluoride make a difference? J Orthod. 2004;31:235-42.
- Petrie A, Sabin C. Medical Statistics at a Glance. 3rd edOxford. Blackwell; 2009.
- 29. Tufekci E, Dixon JS, Gunsolley J, Lindauer SJ. Prevalence of white spot lesions during orthodontic treatment with fixed appliances. The Angle Orthodontist. 2011;81:206-10.
- 30. Singh S, Singh SP, Goyal A, Utreja AK, Jena AK. Effects of various remineralizing agents on the outcome of post-orthodontic white spot lesions (WSLs): a clinical trial. Prog Orthod. 2016;17:1-8.
- 31. Lapenaite E, Lopatiene K, Ragauskaite A. Prevention and treatment of white spot lesions during and after fixed orthodontic treatment: A systematic. Stomatologija. 2016;18:3-8.
- 32. Milly H, Festy F, Andiappan M, Watson TF, Thompson I, Banerjee A. Surface preconditioning with bioactive glass air-abrasion can enhance enamel white spot lesion remineralization. Dental Materials. 2015;31:522-33.
- 33. Zhang J, Boyes V, Festy F, Lynch RJ, Watson TF, Banerjee A. In-vitro subsurface remineralisation of artificial enamel white spot lesions pre-treated with chitosan. Dental Materials. 2018;34:1154-67.
- 34. Mattousch T, Van Der Veen M, Zentner A. Caries lesions after orthodontic treatment followed by quantitative light-induced fluorescence: a 2-year follow-up. The European Journal of Orthodontics. 2007;29:294-8.
- 35. He T, Li X, Dong Y, Zhang N, Zhong Y, Yin W, et al. Comparative assessment of fluoride varnish and fluoride film for remineralization of postorthodontic white spot lesions in adolescents and adults over a 6-month period: A single-center, randomized controlled clinical trial. American Journal of Orthodontics and Dentofacial Orthopedics. 2016;149:810-9.

- 36. Pinelli C, Serra MC, Loffredo LdCM. Validity and reproducibility of a laser fluorescence system for detecting the activity of white-spot lesions on free smooth surfaces in vivo. Caries research. 2002;36:19-24.
- 37. Fernandez-Ferrer L, Vicente-Ruiz M, Garcia-Sanz V, Montiel-Company JM, Paredes-Gallardo V, Almerich-Silla JM, et al. Enamel remineralization therapies for treating postorthodontic white-spot lesions: A systematic review. J Am Dent Assoc. 2018;149:778-86. e2.
- 38. Lopatiene K, Borisovaite M, Lapenaite E. Prevention and treatment of white spot lesions during and after treatment with fixed orthodontic appliances: a systematic literature review. Journal of oral & maxillofacial research. 2016;7.
- 39. Mehta AB, Kumari V, Jose R, Izadikhah V. Remineralization potential of bioactive glass and casein phosphopeptide-amorphous calcium phosphate on initial carious lesion: An in-vitro pH-cycling study. Journal of conservative dentistry: JCD. 2014;17:3.
- Andersson Ö, Kangasniemi I. Calcium phosphate formation at the surface of bioactive glass in vitro. J Biomed Mater Res. 1991;25:1019-30.
- 41. Taha AA, Patel MP, Hill RG, Fleming PS. The effect of bioactive glasses on enamel remineralization: A systematic review. Journal of dentistry. 2017;67:9-17.