Clin Oral Invest (2011) 15:369–373
DOI 10.1007/s00784-010-0401-2

ORIGINAL ARTICLE

Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilised amorphous calcium phosphate

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Received: 4 November 2009 / Accepted: 25 February 2010 / Published online: 10 April 2010

Abstract This study aims to investigate the effect of topical applications of 10% casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) on white spot lesions (WSL) detected after treatment with fixed orthodontic appliances. Sixty healthy adolescents with ≥1 clinically visible WSL at debonding were recruited and randomly allocated to a randomised controlled trial with two parallel groups. The intervention group was instructed to topically apply a CPP–ACP -containing agent (Tooth Mousse, GC Europe) once daily and the subjects of the control group brushed their teeth with standard fluoride toothpaste. The intervention period was 4 weeks and the endpoints were quantitative light-induced fluorescence (QLF) on buccal surfaces of the upper incisors, cuspids and first premolars and visual scoring from digital photos. The attrition rate was 15%, mostly due to technical errors, and 327 lesions were included in the final evaluation. A statistically significant ($p<0.05$) regression of the WSL was disclosed in both study groups compared to baseline, but there was no difference between the groups. The mean area of the lesions decreased by 58% in the CPP–ACP group and 26% in the fluoride group ($p=0.06$). The QLF findings were largely reflected by the clinical scores. No side effects were reported. Topical treatment of white spot lesions after debonding of orthodontic appliances with a casein phosphopeptide-stabilised amorphous calcium phosphate agent resulted in significantly reduced fluorescence and a reduced area of the lesions after 4 weeks as assessed by QLF. The improvement was however not superior to the "natural" regression following daily use of fluoride toothpaste.

Keywords Adolescents · Casein derivate · Orthodontics · Fixed appliances · Remineralisation

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Introduction

The development of white spot lesions is a significant problem during orthodontic treatment with fixed appliances and various preventive measures have been suggested to minimise the incidence [1]. Although there is good evidence to suggest local fluoride exposure as most effective for white spot lesion prevention [2, 3], less is known as to how the lesions should be managed or treated once they have occurred [4]. In recent years, calcium phosphate-based remineralisation technologies have shown

promising results as adjunctive treatments to fluoride therapy in non-invasive management of early caries lesions [5, 6] albeit clinical studies still are sparse [7]. It has been shown that casein phosphopeptides (CPP) have the capacity to stabilise calcium phosphate in solution through binding amorphous calcium phosphate (ACP) to their multiple phosphoserine residues forming small CPP–ACP clusters [5]. Thus, the beneficial effects of CPP–ACP may be attributed to an increased salivary buffering effect which may lead to a suppression of demineralisation and enhancement of remineralisation or, most likely, combinations of both. Previous studies in orthodontic settings have displayed reduced demineralisation around orthodontic brackets in vitro [8] and visual regression of white spot lesions following topical applications of agents containing CPP–ACP complexes in vivo [9, 10]. Further studies are however needed to investigate and clarify the clinical role of the calcium-based remineralisation systems. The aim of the present study was therefore to investigate the effect of daily applications of 10% casein phosphopeptide amorphous calcium phosphate on white spot lesions detected after treatment with fixed orthodontic appliances with the aid of quantitative light-induced fluorescence. The null hypothesis was that the changes in proportional fluorescence would not differ from a control group with standard use of fluoride toothpaste.

Materials and methods

Study group

Sixty healthy patients (27 boys and 33 girls) with at least one labial white spot lesion within the enamel, clinically visible at debonding of fixed orthodontic appliances, were recruited and invited to participate in the project. Both the subjects and their parents received verbal and written information and signed a consent protocol. The exclusion criteria were (a) ongoing medication for a chronic disease and (b) not assessed with high caries risk behaviour. A power calculation based on the QLF data (percent average "change in fluorescence") from a previous trial [11] revealed that 25 subjects would be needed in each group to detect a 20% difference between an intervention and a control group with α- and β-values set at 0.05 and 0.2, respectively. All subjects lived in a community with a low fluoride level in the piped water supply (<0.2 ppm F). Two subjects dropped out during the study period and the QLF images were unreadable in another eight subjects; so, the final material consisted of 50 adolescents of both sexes, 22 in the intervention group and 28 in the control group. The mean age was 15.2 years (range 13–18 years) in both groups.

Study design

The prospective study had a randomised, single-blind, controlled design with two parallel groups. The protocol was approved by the regional ethical committee (Region Hovedstaden, H-A-2007-0081). The subjects were allocated to one of the two groups as determined with aid of computer randomisation. The primary endpoint measure was quantitative light-induced fluorescence readings performed at baseline and after 4 weeks and the secondary endpoint was a clinical four-step score as described below. The relatively short intervention period was chosen as the main regression of WSL is likely to take place immediately after debonding [9]. The researchers responsible for the study and evaluating the endpoints were not involved in the clinical work and blinded for the group assignment.

Intervention

The subjects of the intervention group was instructed to locally apply a standardised amount (approx. 1 g) of a CPP–ACP cream (Tooth Mousse, GC Europe N. V., Leuven, Belgium) to the teeth once daily (in the evening) for a period of 4 weeks and to brush their teeth with a standard fluoride toothpaste (Colgate, 1,100 ppm F) in the morning. Those in the control group were informed and encouraged to use the fluoride toothpaste two times a day (morning and evening) during the study period. Both products were distributed to the subjects at baseline and they were asked to refrain from additional preventive measures based on fluoride during the experimental period.

Clinical registration

A series of three facial digital photographs was exposed at baseline and after 4 weeks for visual inspection of the white spots included for registrations. The slides were scored independently by two examiners according to Gorelic et al. [12]. The labial surfaces of the upper incisors, cuspids and the first premolar were scored as: 1 = no white spot formation, 2 = slight white spot formation (thin rim), 3 = excessive white spot formation (thicker bands) and 4 = white spot formation with cavity formation. In case of disagreement, a consensus was reached.

QLF measurements

The QLF measurements have previously been described in detail [11, 13]. After thorough cleaning with a rubber cup and polishing paste (RD40, Ivoclar Vivadent, Schaan, Liechtenstein) followed by a water rinse, the handpiece of the QLF device was applied at the selected sites and a subsequent image was exposed and stored on a hard disc.

Table 1 Change in fluorescence (ΔF, %) and lesion area (A, mm^2) at baseline and at the end of the intervention. Values in table denote mean (SD) and the number of units are based on individuals

Time	Intervention group (n=22)		Control group (n=28)	
	ΔF, %	A, mm^2	ΔF, %	A, mm^2
Baseline	6.68 (0.58)	0.12 (0.16)	7.04 (1.65)	0.19 (0.43)
4 weeks	4.45[a] (1.82)	0.05[a] (0.09)	4.51[a] (2.46)	0.14 (0.31)
95% CI of the difference	1.46–3.01	0.02–0.13	1.90–3.14	-0.04–0.10

[a] Statistically significant difference compared with baseline (p<0.05, paired test)

The procedure was repeated with the same position at the follow-up visits after 4 weeks. The final evaluation with image subtraction and quantification of mineral content was done afterwards by two of the investigators blinded for the group assignment. A total number of 327 white spot lesions were analysed at baseline and follow-up with a mean value of six lesions per subject. An inter- and intra-examiner reliability test was performed by a re-evaluation of a random sample (10%) of the material.

Statistical methods

All data were processed with the SPSS software (version 17.0, Chicago, IL, USA). The follow-up mineral content was compared with baseline within each group with the aid of ANOVA for repeated measurements. The comparisons between the groups were computed by Student's t-test or a chi-square test. All data were checked for normality distribution. Concerning the QLF data, a mean value of all included sites in each subject was calculated in order to use the patient as a unit. The reproducibility and repeatability (reliability) of the QLF analysis was calculated by intra-class correlation coefficient (ICC). A p-value less than 0.05 was considered as statistically significant.

Results

The results of the quantitative light-induced fluorescence measurements are summarised in Table 1. The baseline ΔF values were similar in the intervention and control groups at baseline and statistically significant (p<0.05) reductions of approximately 30–35% were disclosed in both study groups after the 4-week experimental period. The lesion area (A, mm^2) was somewhat larger in the control group than in the intervention group at baseline, but the difference was not statistically significant. After the study period, the average lesion area was decreased by 58% in the CPP–ACP group and by 26% in the control group, which was significantly different to baseline in the intervention group (p<0.05). Concerning the lesion area, the difference between the groups at follow-up was close to reaching statistical significance (p=0.06). The intra-examiner ICC values for the two examiners were 0.93 and 0.94, respectively. The corresponding value for the inter-examiner test was 0.90.

The clinical scores at baseline and after 4 weeks are shown in Table 2. At baseline, the prevalence of WSL (score >1) was 84.6% in the intervention group and 85.1% in the control group. The corresponding figures after the study period were 52.3% and 47.3%, respectively. There were no statistically significant differences between the groups. No side or adverse effects were reported in connection with the study.

Discussion

The present study was designed as a superiority test to investigate whether or not the novel casein phosphate-based remineralisation concept was more beneficial than "natural" remineralisation with fluoride toothpaste. Both treatments resulted in significant improvements in change of fluorescence and visual scores compared to baseline, but no significant differences were detected between the groups. Thus, the null hypothesis could not be rejected. However,

Table 2 Percentage distribution of clinical scores at baseline and at the end of the intervention. The scores are defined in the text. n denotes the number of readable facial sites on upper incisors, cuspids and first premolars

Time	Intervention group (n=132)				Control group (n=180)			
	1	2	3	4	1	2	3	4
Baseline	15.4	54.2	29.5	0.9	14.9	59.0	25.0	1.1
12 weeks	47.7	37.1	15.2	–	52.7	36.1	10.6	0.6

this does not necessarily mean that the two treatments were equal; an equality test would require a substantially larger study group. There was a clear but non-significant tendency of a greater reduction in lesion area in the CPP–ACP group. This may partly be explained by the fact that both the clinical scoring and QLF measurements indicated that the white spot lesions were slightly more severe in the control group at baseline.

The results from this clinical trial was novel but yet expected. There is good evidence that casein phosphopeptide–amorphous calcium phosphate can remineralise subsurface enamel lesions [6, 14], and recent studies have indicated a beneficial effect on demineralisation of enamel adjacent to orthodontic brackets [8–10, 15]. It is however important to underline that the present study was not placebo-controlled and that the relative influence of the presence of fluoride in the intervention group was unclear. Due to the strong evidence revealed in systematic reviews [2, 16], it was not considered as "best clinical practice" to totally omit the use of fluoride toothpaste in the intervention group, especially in the light of orthodontic patients with fixed appliances and who are thought to be patients at risk for enamel demineralisation. The mechanism of action may very well be a combination of CPP–ACP and fluoride [6], but from a clinical point of view it was of interest to find that this mix, within limitations and short duration of this study, was not superior to fluoride toothpaste alone. Interestingly, CPP–ACP products are now commercially available with fluoride as adjunctive therapy in the non-invasive management of early caries lesions [5]. One should also keep in mind that the intervention period was also relatively short and further changes in the WSL scores cannot be ruled out [9]. Nevertheless, the fluoride-free CPP–ACP concept seems to be a good alternative for lesion regression in patient groups reluctant to fluoride products due to parental safety concerns.

The intervention group suffered from a somewhat higher attrition rate than the control group. This was unintentional and there was no obvious explanation for this. The main reason for exclusion was that a relatively high number of the QLF images had to be omitted due to technical errors such as ambient light (17.7%). Other problems were dark or not sharp images and angulation errors (3%). Almost 10% of the registrations were excluded in spite of acceptable quality due to the fact that images, either baseline or at follow-up, were compromised, which made the pair-wise comparison impossible. QLF has previously been used to investigate de- and remineralisation adjacent to orthodontic appliances, and an actual correlation with mineral loss of approximately r=0.8 has been reported [17, 18]. However some concerns have recently been raised for its use in vivo within orthodontics. The forced and wanted movement of teeth makes it almost impossible to provide such congruent images that are required by the QLF software [19]. This was however not a problem in our study since the registrations were conducted after debonding during the retention period. The QLF findings were relatively well reflected by the clinical scores although it should be noted that the ordinal index of Gorelic et al. [12] only addresses the severity of WSL but not the area of the tooth covered by the white spot. It should also be stressed that the dropout numbers were comparatively high (20–25%) also for the visual readings due to technical problems. Based on the personal interviews, we had all reasons to believe that the subjects complied with the study protocol and no side effects or complaints were registered in connection with the trial.

In conclusion, topical treatment of white spot lesions after debonding of orthodontic appliances with a casein phosphopeptide-stabilised amorphous calcium phosphate agent resulted in significantly reduced ΔF values and a reduced area of the lesions after 4 weeks as assessed by quantitative light-induced fluorescence. The improvement was however not superior to "natural" regression with daily use of fluoride toothpaste.

Acknowledgement The study was partly supported by a grant from GC Europe (Belgium) who also provided the test product. The authors would like to thank Pia Hole, Marianne Knudsen, Birgitte Kristensen and Mirko Zelic for their skilful clinical and technical work.

Conflicts of interest The authors declare that they have no conflict of interest. The authors alone are responsible for the performance and evaluation of the study protocol as well as for the content and writing of the paper.

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