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Clinical Evaluation of Treatment of White Spot Lesions with Icon

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CLINICAL EVALUATION OF TREATMENT OF WHITE SPOT LESIONS WITH ICON

by

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ABSTRACT

Introduction: Despite an increased awareness by clinicians and their attempt to aid patients in the prevention of white spot lesions, enamel demineralization continues to be a problem associated with orthodontic treatment. Current treatment options for these unaesthetic scars on the teeth range from conservative options for remineralization such as the use of fluoride and CPP-ACP to more aggressive treatment involving loss of tooth structure with microabrasion or restorations. An innovative option for treatment has recently been introduced in the form of the infiltrant resin, Icon. Icon infiltration is a minimally invasive procedure performed by a dentist that is claimed to penetrate and fill the porosities of lesions with a light-cured resin material. This treatment has the potential to mask white spot lesions by occluding porosities and restoring natural optical properties of the enamel. The aim of this study was to evaluate the immediate and short term effect of Icon in masking post-orthodontic white spot lesions. **Material and Methods:** Eleven patients with post-orthodontic white spot lesions were recruited for this randomized controlled clinical trial utilizing a split-mouth design. Premolar and anterior teeth on the treatment side of the mouth were treated with Icon according to the manufacturer's instructions. Teeth on the opposite side of the mouth were used as controls. Intraoral photographs were taken of control and treated teeth before treatment (T1), after treatment (T2), and four to six weeks after treatment (T3). A modified Enamel Decalcification Index was used to score lesions at all timepoints. **Results:** From T1 to T2, 36.46% of

treated lesions decreased by one or more lesion grade compared to only 7.29% of the non-treated lesions ($p<0.0001$). Over the course of the study period (i.e. T1-T3), 45.57% of treated lesions decreased in grade compared to 6.25% of non-treated lesions. Furthermore, Icon treatment resulted in a total masking effect of 24% of lesions. This difference was statistically significant ($p<0.0001$). **Conclusions:** Icon treatment decreased the size of many post-orthodontic white spot lesions compared to untreated controls. Icon infiltration provides a unique treatment option for patients that allows them to achieve immediate masking of lesions with no long-term compliance necessary.

Keywords: white spot lesion, demineralization, Icon, infiltrant

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CI	confidence interval
CPP-ACFP	casein phosphopeptide-amorphous calcium fluorophosphate
CPP-ACP	casein phosphopeptide-amorphous calcium phosphate
EDI	enamel decalcification index
GEE	generalized estimating equation
IQR	interquartile range
MFP	monofluorophosphate
PPM	parts per million
OR	odds ratio
QLF	quantitative light-induced fluorescence

INTRODUCTION

White Spot Lesions and the Caries Process

A functionally acceptable and stable orthodontic treatment result can often be "scarred" by the presence of white spots on the teeth. These white spots usually appear as a ring around the position of a previous bracket or band. White spot lesions are clinically visible signs of demineralization of tooth structure. The caries process, in general, involves loss of minerals from the tooth due to metabolic events in biofilms or bacterial plaque. This loss leaves porosities in the enamel which change the optical properties giving the opaque, white appearance. White spot lesions are often referred to as early or incipient lesions; however, this is not always an accurate description of the lesions. White spot lesions may be the first sign of new caries, but it can also be an arrested lesion that has been present for many years.[1,2]

Bacteria in dental plaque are the main culprits in the development of white spot lesions. The role of mutans streptococci in the development of caries has been extensively researched.[3,4 5,6] These cariogenic bacteria such as *Streptococcus mutans* and *lactobacilli* produce acids when they metabolize fermentable carbohydrates.[3,7] The acids enter into the pores of the enamel and dissociate producing hydrogen ions that dissolve the mineral content into free calcium and phosphate ions. These ions can then diffuse out of the tooth leaving microporosities behind.[8,9] If this demineralization process continues or is not reversed via remineralization, a white spot lesion and/or caries can result.

Orthodontic appliances including brackets, bands, coils, etc. can provide more plaque-retentive areas for bacteria to thrive. Lundstrom and Krasse found an increase in the number of cariogenic bacteria among orthodontic patients.[10] This increase in bacteria can put orthodontic patients at an even higher risk for caries.

Many studies have sought to determine the incidence of white spot lesions after orthodontic treatment; however, the results are highly variable and range from 15 to 89%.[11] The most recent report on this topic showed that 72.9% of orthodontic patients developed one or more new lesions during treatment.[12] This inconsistency may arise from several different aspects of these studies. White spot lesions are difficult to quantify *in vivo* and also difficult to distinguish from other tooth opacities including developmental discolorations and fluorosis. Thus, there are also contradictions in the literature as to whether there is an increase in prevalence among post-orthodontic patients compared to untreated persons.

Although white spot lesions may occur in any person with improper oral hygiene, several studies have found a significant increase in the prevalence and/or severity of these lesions among orthodontic patients. Mizrahi found an increase in both prevalence and total surface area of white spot lesions with post-orthodontic patients having 84% of teeth with lesions and an Opacity Index of 0.200 compared to a group of untreated controls having 72.3% of teeth with lesions and an Opacity Index of 0.125. In this study the Opacity Index was scored for vertical thirds of each tooth from 0 to 3, with 0 as having no opacity, 1 as opacity covering 1/3 of the area, 2 as opacity covering from 1/3 to 2/3 of the area, and 3 as opacity covering from 2/3 to the entire area.[13] In a separate study, Mizrahi found a significant difference in prevalence and severity of enamel opacities

before and after orthodontic treatment. He reported the greatest differences on the cervical and middle thirds of the vestibular surfaces of maxillary and mandibular first molars, maxillary lateral incisors, and mandibular lateral incisors and canines.[14] Similarly, Gorelick found an overall increase in number of white spot lesions among post-orthodontic patients compared to controls. The maxillary lateral incisors had the highest incidence of lesions upon bonding as well as banding.[15] A more recent study conducted in 1989 found not only an increase in the number of lesions among post-orthodontic patients, but also that these lesions were still present five years after the conclusion of treatment. They hypothesized that these lesions may have remineralized on the surface when exposed to normal daily fluoride levels, but the subsurface lesions remained leaving the opacity that seemed to be resistant to further remineralization.[16]

Another study, however, found that orthodontic treatment did not contribute to an increase in prevalence of lesions but did affect localization of caries. Zachrisson and Zachrisson showed a different pattern of demineralization with the vestibular and lingual areas more prone than the interproximal areas on teeth with orthodontic bands. They concluded that bands decreased susceptibility in areas that were fully covered while increasing susceptibility in partially covered areas of the teeth.[17]

Perhaps even more shocking than the widely debated prevalence of the lesions is the short time frame in which this demineralization process can occur. O'Reilly and Featherstone found that measurable demineralization was observed in as little as one month after bonding even with the use of a fluoride toothpaste. Although not clinically visible, they reported up to a 15% mineral loss both occlusal and cervical to orthodontic brackets in this short time period.[18] Just one year later, Ogaard published data showing

that visible white spot lesions can develop in as little as four weeks under ill-fitting orthodontic bands.[19] With an average of four to six weeks between orthodontic appointments, it is possible for patients to develop these lesions before even the first post-bonding evaluation.

White Spot Lesion Prevention

Prevention of white spot lesions among orthodontic patients is very important, and much research has been dedicated to finding the best techniques for patients and clinicians. Prevention protocols range from pre-bonding sealants such as Pro-Seal to fluoride varnishes applied at monthly visits. Zachrisson concluded in 1976 that despite definite risks of orthodontic treatment, damage to teeth and supporting tissues can be avoided when accepted orthodontic principles are followed in conjunction with good oral hygiene and use of fluoride by the patient.[20] Richter found in 2011, however, that there was no association between the recommended fluoride protocol to the patient and development of white spot lesions. Likely, this had less to do with an inadequate recommended fluoride regimen and more to do with noncompliance by the patient.[12] Unfortunately despite efforts among researchers and clinicians, many patients continue to develop these unaesthetic lesions following orthodontic treatment. Furthermore, Mattousch et al found that post-orthodontic white spot lesions have a very limited ability to improve without treatment even after appliance removal. The authors reported that less than three percent of lesions remineralized completely after two years. They found the greatest magnitude of remineralization in the first six months after debonding; however,

lesions still visible after this time did not disappear within the next year and a half of follow-up. In summary, only 40% of the lesions showed any amount of improvement, with the majority remaining stable and 15% worsening over the two-year period in this study.[21] Thus, it is necessary to investigate ways to treat these lesions. Ideal treatment of the lesions should accomplish the following: remineralize weakened tooth structure, arrest the decay process, mask the opacity, and require little to no patient compliance. The last goal of requiring little patient compliance is important when you consider how the lesions develop in the first place. White spot lesions do, after all, only develop with the necessary plaque accumulation present on many patients' teeth. Had the patient been compliant with recommendations of proper oral hygiene and fluoride use during orthodontic therapy, there would be no lesions to treat upon removal of appliances.

White Spot Lesion Treatment

When prevention of white spot lesions is unsuccessful, finding the most appropriate treatment for the lesions is now necessary. Although there are numerous treatment modalities with various advantages and disadvantages, it is important to find the treatment that will provide the desired results, is efficient, and is as conservative as possible. Although most white spot lesions can be removed or masked by a restoration, veneer, or crown, the clinician must determine if this is the most conservative approach that can achieve the desired results.

Remineralization is the process of redeposition of minerals into enamel. Calcium fluoride, the major reaction product of topical fluoride agents, can be incorporated into

the deficient areas forming fluoroapatite.[22] Fluoride from topical sources speeds up the remineralization process by incorporating into the surface as fluorapatite and attracting calcium and phosphate ions. This new fluorapatite surface has a much lower solubility than hydroxyapatite and can resist further demineralization.[23] The formation of one unit cell of fluorapatite requires two fluoride ions, ten calcium ions, and six phosphate ions; thus, the availability of calcium and phosphate ions can be the limiting factor for net remineralization to occur.[24]

Fluoride

Many questions arise when considering the use of fluoride to remineralize white spot lesions. What is the most effective delivery method? What is the most effective fluoride form and concentration? What are the esthetic effects of remineralization with fluoride? Many studies have sought to answer these and other questions surrounding the use of what is often referred to as the "treatment of choice" for early caries.

There are many delivery methods for fluoride ranging from natural and city water supplies to topical agents such as varnishes, pastes, and rinses. In 1991, Barbakow et al recommended the use of low concentration fluoride dentrifices (0.10%-0.15%) and rinses (0.02%-0.05%) in combination with the application of topical fluorides (up to 1.23%) at regular dental visits.[25] Remineralization by fluoride can occur using sodium fluoride (NaF) or sodium monofluorophosphate (MFP); however, several studies have shown that these two forms of fluoride react differently with enamel and have different mechanisms of action in the remineralization process. Fluoride is incorporated into enamel by

replacement of the hydroxyl group in the apatite crystal;[26,27] while sodium monofluorophosphate acts by replacing a phospate group with the MFP.[28,29] Slater et al found that MFP promoted remineralization primarily in the surface layer; whereas, sodium fluoride had more of an effect in the body of the lesion. These differences in sodium fluoride and MFP may provide for a greater remineralization potential when the two forms are used together.[30] Mellberg and Mallon compared the effect of MFP and NaF at concentrations of 75-900 parts per million (ppm) used alone and in combination. Measurement of remineralization using microradiographs showed that the combination of NaF/MFP (75/225 ppm) had the greatest remineralization potential confirming that the different mechanisms of action may be beneficial in combination.[31] Mellberg et al found that a dentrifice containing 1000 ppm sodium monofluorophosphate was successful in prevention of further demineralization in addition to promoting remineralization of artificial caries lesions. Overall, 75% of the lesions brushed with the experimental dentrifice showed a net mineral gain, while 60% of the lesions in the placebo group had a net mineral loss.[32] Linton found that an experimental fluoride mouthrinse (50 ppm) was more effective in reducing the size of artificially created white spot lesions than a commercially available mouthrinse containing 225 ppm fluoride.[33] Another study found a low concentration fluoride varnish, Fluor protector at 1000 ppm, to be superior in remineralization compared to professional cleaning alone. Using quantified light-induced fluorescence, Tranæus et al concluded that application of this low concentration varnish every six weeks for six months had a favorable effect on the remineralization process. Quantitative light-induced fluorescence (QLF) was able to detect a decrease in lesion area and an increase in remineralization in the varnish group; however, none of the changes

were clinically detectable upon visual inspection.[34] Buchalla found that a single application of a highly concentrated fluoride solution (10,000 ppm) increased the overall fluoride content of a lesion *in situ*. They measured both the KOH-soluble fluoride and the structurally bound fluoride of demineralized areas immediately upon application and after one, two, three, and four weeks *in situ*. The highly fluoridated solution promoted higher KOH-soluble fluoride and structurally bound fluoride levels for all time points with the soluble fluoride decreasing and the bound fluoride increasing over time.[35] Willmot compared the reduction in size of post-orthodontic lesions among patients either using a low-dose (50 ppm) fluoride mouthrinse or a non-fluoride rinse. In this *in vivo* study, he found that white spot lesions generally were reduced in size by 30% with or without the use of a low-dose fluoride rinse.[36] While several studies have shown the effect of fluoride on relatively newly formed white spot lesions, Zanter found that toothpastes containing either sodium fluoride (1500 ppm) or amine fluoride (1250 ppm) had no measureable effect on lesions that have been present for at least five years.[37] Sano found that a toothpaste containing a combination of 500 ppm fluoride and 5% xylitol provided superior remineralization compared to either control dentrifices without NaF or xylitol or pastes with only 500 ppm fluoride.[38] Several other studies have indicated the usefulness of xylitol as an inductive agent by facilitating the movement and accessibility of Ca^{2+} into deeper layers of demineralized enamel.[39-43] Ferreira et al compared two fluoride varnishes, 5% NaF and 6% NaF + 6% CaF_2, and found them equally successful in reducing the size of white spot lesions *in vivo*. Both varnishes resulted in a clinically significant change in size of approximately 60% of treated lesions.[44] Another study concluded that a monthly application of a 5% NaF varnish for six months is effective in

reversing white spot lesions. This study, however, used a DIAGNOdent pen to measure the lesion and reduction which does not give any information on size of the lesion or esthetic effects.[45]

In treatment of white spot lesions, several factors must be considered. As many of the above studies examined, the amount of remineralization is an important factor. Equally important, however, is the esthetic effect of the treatment and the patient's perceived improvement. While many studies have found fluoride to be an effective remineralizing agent, few studies have examined the esthetic effects of such treatment. In 2008, Bishara found that immediate application of high concentration fluorides may only remineralize the superficial enamel layer allowing the deeper porosity to still affect the opacity index, thus leaving the unaesthetic "white spot". Although high fluoride doses may completely arrest the caries process and be acceptable for posterior lesions, for white spot lesions posing an esthetic concern it may be advisable to allow lower concentration calcium and fluoride ions from the saliva or dentrifice to penetrate deeper into the lesion.[46] Despite the numerous studies examining fluoride in the treatment of white spot lesions, no consensus has been reached as to the most effective and efficient treatment method to address both the loss of minerals and esthetic concerns of these carious lesions.

Microabrasion

Enamel microabrasion is a technique that has been used in the treatment of enamel discoloration since the mid-1980s. Much of the research on microabrasion has

been completed by Theodore Croll who has experimented with microabrasion in treating various enamel discolorations including fluorosis in order to determine the best technique to achieve the ideal esthetic results. In 1989, Croll along with Premier Dental Products introduced a product called Préma Compound which contains a mild concentration of hydrochloric acid blended with fine-grit silicon carbide particles in a water-soluble paste. Initially, it was recommended to use a concentration of 18% hydrochloric acid; however, Croll now recommends an 11% acid paste that is more tissue-friendly. The technique developed by Croll includes an initial pumice cleaning and rubber dam isolation followed by one-minute intervals of microabrasion using the paste on a slow-speed handpiece. This application can be repeated as necessary to achieve the desired result keeping in mind the overall thickness of the enamel.[47-52] Waggoner found that the initial one minute application results in the irreversible loss of approximately 12 μm of enamel with an additional 26 μm lost with each subsequent application.[53] One of the challenges in this procedure is estimating the depth of the initial lesion to determine if this procedure will be effective. Since microabrasion results in permanent loss of enamel, if the lesion depth is greater than the amount of enamel that can be sacrificed this procedure is not the treatment of choice. Furthermore if too much enamel is lost exposing or nearly exposing dentin, the tooth may appear too yellow for the patient's satisfaction. In this situation, Croll recommends considering external bleaching following microabrasion in order to obtain a pleasing result.[51] Another author recommends following microabrasion with an in office application of CPP-ACP and a subsequent at-home application protocol in order to achieve the desired esthetic results.[54] Despite the numerous papers published on this technique, no randomized clinical trial has been completed examining the effect of this

technique on achieving esthetic results with enamel discolorations of any type. Currently available research is based on numerous case studies that have given rise to the microabrasion technique that is often used in offices today.

Casein Phosphopeptide-Amorphous Calcium Phosphate

As stated above, demineralization involves the loss of calcium and phosphate ions from enamel due to a microbiologic and acidic challenge. Unfortunately the use of calcium phosphates to remineralize enamel has not been successful because the soluble ions are not retained on the tooth surface in concentrations high enough to promote diffusion into the enamel.[55] Through his studies examining the anticariogenicity of milk derivatives, Reynolds found that the casein phosphopeptides had the ability to stabilize calcium and phosphate ions at the tooth surface, thus maintaining high concentration gradients of calcium and phosphate ions favoring remineralization. This stabilization product has come to be known as casein phosphopeptide-amorphous calcium phosphate or CPP-ACP. In 1997, Reynolds found that the complex is successful in remineralizing subsurface lesions at concentrations of 0.5% and 1.0% *in vitro*.[56]

CPP-ACP complex was patented by Reynolds and the University of Melbourne, Australia along with the Victorian Dairy Industry Authority in 1991. Since its introduction as an agent used not only to prevent demineralization but also to increase remineralization, CPP-ACP has been incorporated into several products including a commercially available sugar-free chewing gum (Recaldent™; GC Corp, Japan and Trident White®; Cadbury Adams USA, Parsippany, NJ, USA), mints (Recaldent

Mints™; Cadbury Japan Ltd, Japan), topical gels (Tooth Mousse™, Tooth Mousse Plus; GC Corp, Japan and MI Paste and MI Paste Plus; GC America, Alsip III) and experimental sports drinks and glass ionomer cements.[57]

In 2001, Shen et al evaluated the potential of chewing gums containing CPP-ACP to remineralize subsurface lesions *in situ*. The participants used the chewing gum for 20 minutes, four times per day for 14 days after which the enamel blocks were evaluated using microradiographic analyses and computerized imaging software. The study found that the addition of CPP-ACP to either sorbitol- or xylitol-based gums at 10.0, 18.8, or 56.4 mg increased remineralization an average of 63%, 102%, and 152%, respectively, relative to the control gum.[58] Similar results were found by the same group in 2003;[59] while another study found no increase in remineralization with gums containing various forms of calcium including CPP-ACP compared to non-calcium containing gums.[60] Furthermore, Iijima et al found that chewing gum containing 18.8 mg CPP-ACP produced approximately twice the level of remineralization compared to the control gum and that the remineralized enamel had superior resistance to further demineralization.[61] More recent studies by the Reynolds group confirmed the increased remineralization effect of chewing gums containing CPP-ACP over those containing other forms of calcium or no calcium.[62,63]

Cai et al evaluated the reminalization potential of CPP-ACP in mint/lozenge form in 2003. The study compared lozenges containing 56.4mg and 18.8 mg CPP-ACP to lozenges containing no CPP-ACP. After consuming four lozenges per day for 14 days, this *in situ* study found that the lozenges containing CPP-ACP increased remineralization by 176% and 78%, respectively, compared to the control lozenge. Thus like the above

chewing gums, the Reynolds group found the lozenges to be an effective method of remineralization for subsurface enamel lesions.[64]

Since the discovery of of CPP-ACP as an effective remineralization agent, much of the available research has focused on the use of topical gels and pastes containing the complex. Rahiotis and Vougiouklakis found that specimens treated with Tooth Mousse GC had a 74.4% increase in remineralization compared with controls *in vitro*.[65] Tooth Mousse GC has also been reported to be an effective agent in conjunction with microabrasion in the treatment of white spot lesions.[54] In an *in vivo* study, Andersson compared two treatment protocols for post-orthodontic white spot lesions: A) daily applications of a dental cream containing CPP-ACP for three months followed by a three-month period of daily toothbrushing with a fluoridated dentrifice and B) daily rinse with a 0.05% sodium fluoride mouthwash combined with a fluoridated dentrifice for six months. There was a significant improvement in the clinical appearance of the white spot lesion for both groups; however, the CPP-ACP regimen resulted in a higher complete disappearance of lesions after 12 months (63% compared to 25%).[66] In 2008, Kumar et al conducted an *in vitro* study in which they compared a fluoridated toothpaste (1100 ppm), a non-fluoridated toothpaste, and Tooth Mousse as a toothpaste, as a topical coating, and as a topical coating after the fluoridated toothpaste. They found the greatest decrease in lesion depth when CPP-ACP was used as a topical coating following the use of the fluoridated toothpaste.[67] Bailey et al conducted a clinical trial in post-orthodontic patients using fluoride toothpastes and receiving supervised fluoride mouthrinses to test whether there was an increase in remineralization among participants using Tooth Mousse compared with a placebo cream (without CPP-ACP). The participants were

instructed to apply one gram of the cream to the teeth two times per day for 12 weeks after normal oral hygeine procedures using a 1000 ppm fluoridated toothpaste. The participants also received a supervised mouthrinse with 900 ppm NaF at each assessment visit. This study used the ICDAS II method to score lesions at baseline, 4, 8, and 12 weeks. There was a significant increase in regression of lesions in the CPP-ACP group compared to the placebo group, with 31% more lesions showing regression at 12 weeks.[68]

In 2004, Cross et al reported that CPP has the ability to stabilize not only calcium and phosphate ions, but also fluoride ions. They found that these complexes, designated CPP-ACFP have the potential for superior caries prevention compared to CPP-ACP or fluoride alone.[69] It has been shown that CPP can adhere to 25 calcium ions, 15 phosphate ions, and five fluoride ions per molecule.[70] A later study examined the remineralization potential of CPP-ACP with fluoride compared to either of the aforementioned alone. Five dentrifice slurries were prepared: A) placebo, B) 1100 ppm NaF, C) 2800 ppm NaF, D) 2% CPP-ACP, and E) 2% CPP-ACP plus 1100 ppm NaF. Participants received an appliance with enamel slabs containing subsurface lesions and were instructed to rinse with the slurries for 60 seconds, four times per day for 14 days. The enamel slabs were then divided into halves with half of each slab prepared for acid challenge. All half-slabs were then analyzed with microradiography. Fluoride produced dose-dependent remineralization with the 2800-ppm slurry replacing significantly more mineral than the 1100-ppm formulation. The 2% CPP-ACP slurry produced a remineralization level similar to that of the 2800-ppm fluoride slurry, and the slurry of 2% CPP-ACP plus 1100 ppm fluoride was superior to all other formulations. Microradiography revealed that fluoride alone resulted in remineralization of the surface layer, while CPP-ACP alone or

in conjunction with fluoride produced remineralization throughout the body of the lesion. Furthermore, the remineralized enamel appeared to be more resistant to acid challenge in the CPP-ACP plus fluoride group compared with all other formulations.[24] Commercially-available products such as Tooth Mousse Plus and MI Paste Plus reflect this apparent synergistic effect as they contain not only CPP-ACP but also 900 ppm fluoride.[57] A recent randomized controlled trial investigated the effect of MI Paste Plus on both prevention and treatment of white spot lesions in orthodontic patients. This study involved current orthodontic patients randomly divided into treatment and control groups using either MI Paste Plus or a placebo paste one time per day for three months. The study found a decrease of 53.5% in mean lesion score for patients treated with MI Paste Plus compared with an increase of 91.1% in scores among the control group.[71]

Much research has been dedicated to establishing the efficacy of CPP-ACP and CPP-ACFP in the remineralization of white spot lesions; however, like fluoride the product presents with two major shortcomings as a remineralization method. As shown in several studies, remineralization with CPP-ACP can provide esthetic benefits; however, this effect can take weeks to months before clinically visible results are seen. Secondly, all forms of CPP-ACP require compliance by the patient with self administration of chewing gums, lozenges, or pastes.

Infiltrant Resins

An alternative treatment option for arresting and masking white spot lesions is the infiltration of the lesions with low-viscosity light cured resins. Infiltrant resins can fill in

lesion porosities and occlude cariogenic pathways thus stopping progression of the lesion and restoring normal optical properties. In contrast to fissure sealants where the barrier is placed on the lesion surface, infiltration aims to create a diffusion barrier inside the lesion by replacing lost minerals with resin.[72] Early studies began in the 1970s with experiments involving commercially-available adhesives and sealants. These and other later studies demonstrated that these adhesives and sealants are effective infiltrants of artificially created lesions.[73-77] These studies, however, focused on artificial lesions which may differ from natural lesions not only in their etiology but also in their structure and organic composition. The surface layer of natural enamel lesions has a lower pore volume than the lesion body, so infiltration into the body of the lesion may be hindered by the less porous surface. Natural caries lesions might also be contaminated with organic materials that can hinder resin infiltration.[72] Early studies on artificial lesions utilized the commonly used restorative etch containing 37% phosphoric acid; however, Meyer-Lueckel postulated that this etching procedure may not be effective enough in eroding the surface layer of natural lesions. They found that a 15% hydrochloric acid etch was more effective in surface layer erosion and later confirmed that increased penetration depths were obtained with the new etching technique. The latter study found that even with a two-minute 15% hydrochloric acid etch, the surface layer was not completely eroded in 67% of the lesions, thus recommending consideration of a longer application time.[72,78]

Early studies investigating infiltration using commercially-available adhesives were successful; however, most of these studies used relatively shallow artificially-created lesions. These resin materials are optimized for adhesive purposes and are only limited in their ability to infiltrate subsurface lesions. In 2008, Meyer-Lueckel et al

began testing experimental resin infiltrants to determine their ability to penetrate into deeper subsurface white spot lesions. Penetration of the resins was found to be dependent on the penetration coefficient of the material. The penetration coefficient is derived from the Washburn Equation that describes the penetration of liquids into porous solids through capillary action.[79,80] A study in 2010 showed that one experimental infiltrant was able to penetrate over 600 µm into natural lesions *in vitro.*[81]

In July 2009, Drs. Meyer-Lueckel and Paris out of Germany along with DMG America introduced a commercially-available infiltrant resin in the US. This resin, Icon, is marketed as an option for both prevention and treatment of white spot lesions.

The first *in vivo* study with the infiltrant developed by Meyer-Lueckel was completed in 2010 and involved radiographic determination of the progression of interproximal lesions involving the inner half of enamel up to the outer third of dentin. They found that the infiltrant decreased lesion progression over an eighteen-month period from 37% in controls to 7% in the experimental group.[82] Another study found infiltration in conjunction with fluoride varnish to be superior to fluoride varnish alone in reducing interproximal lesion progression.[83] For treatment of interproximal lesions, establishment that progression of the lesion has been stopped is sufficient; however, labial lesions present with the unique challenge of esthetics as a major concern in addition to lesion progression. Torres et al examined the ability of several white spot lesion treatment modalities to mask the lesions by assessing color change *in vitro*. They determined that Icon was more effective in this regard than either a daily application of a 0.05% fluoride gel or a weekly application of a 2% fluoride gel.[84] In July 2011, Kim et al clinically assessed the effectiveness of masking white spot lesions using Icon. They evaluated color

changes of lesions either determined to be developmental in origin or post-orthodontic decalcification. This study found that 25% of developmental lesions were completely masked, while 35% were partially masked and 40% were unchanged. In comparison, 61% of post-orthodontic lesions were determined to be completely masked with 33% partially masked and 6% unchanged. The authors concluded that the masking effect of Icon is dramatic in some cases but not in others and the effect may vary with lesion type. This study, however, did not have a control group and had no measurement of change in size of the lesion but rather just a general color change before and after treatment.[85]

Present Study

Multiple studies have led to the development of the commercially available infiltration resin, Icon. These studies have demonstrated its usefulness as a treatment method of white spot lesions *in vitro*. Currently available *in vivo* studies are inadequate to prove Icon's ability to mask post-orthodontic white spot lesions clinically. The current study aims to investigate the ability of Icon to reduce, both in size and number, white spot lesions present after orthodontic treatment.

MATERIAL AND METHODS

Study Design

The study protocol was reviewed and approved by the institutional review board of the University of Alabama at Birmingham.

Eleven patients were recruited through the Orthodontic Clinic at the University of Alabama at Birmingham for this prospective randomized clinical trial. All patients were informed of the objectives, risks, and benefits of the study and were required to sign informed consent forms prior to enrollment. All patients had to have a history of orthodontic treatment and the presence of a smooth surface white spot lesion on at least two teeth from central incisor to second premolar in separate quadrants of the mouth. Patients were excluded from the study for the following reasons: (1) presence of any fixed orthodontic appliance on the labial surface of any tooth from second premolar to second premolar, (2) current or planned use of any alternative white spot lesion treatment method during the study period, and (3) current pregnancy. The final patient population consisted of seven (63.6%) males and four (36.4%) females with a mean age of 16.5 years at initial examination.

The study was completed in a split mouth design in which teeth on one side of the mouth were treated with Icon, while teeth on the opposite side of the mouth were used as the control, non-treatment group. Only teeth from second premolar to second premolar

with the presence of a smooth surface labial white spot lesion were included in either the treatment or control groups. Treatment and control sides were divided up by randomly assigning patients to either the right or left side treatment group upon enrollment in the study.

A non-fluoridated pumice was used on a slow-speed handpiece to remove all plaque from the labial surfaces of teeth in treatment and control groups. Liquid rubber dam (Kool-Dam, Pulpdent®, USA) was applied along gingival margins of teeth in the treatment group. Icon was used to treat the labial surfaces of teeth in the treatment group according to the manufacturer's recommendations. Icon-Etch (15% hydrochloric acid) was applied to the tooth surface for two minutes followed by rinsing and drying, and the etching process was repeated a second time. Icon-Dry (ethanol solution) was applied to the tooth surface and allowed to sit for 30 seconds followed by air drying. Icon-Infiltrant was applied to the tooth surface for three minutes. Excess infiltrant was removed from the surface of the tooth using cotton pellets, and then the surface was light cured for 40 seconds. An additional layer of Icon-Infiltrant was applied to the tooth for one minute followed by removal of excess and a 40-second light cure. Rubber dam material was removed, and the tooth surface was polished using an Enhance® polishing point (DENTSPLY/Caulk, USA) on a slow-speed handpiece.

Standardized clinical photographs were taken immediately before treatment (T1), immediately after treatment (T2), and at follow-up four to six weeks after treatment (T3) (Figure 1). Each photo set contained intraoral buccal photos and an intraoral center photo capturing the labial surfaces of the premolars and anterior teeth. All pictures were taken using the same digital camera under controlled clinical settings (Sony DSC-H50, USA).

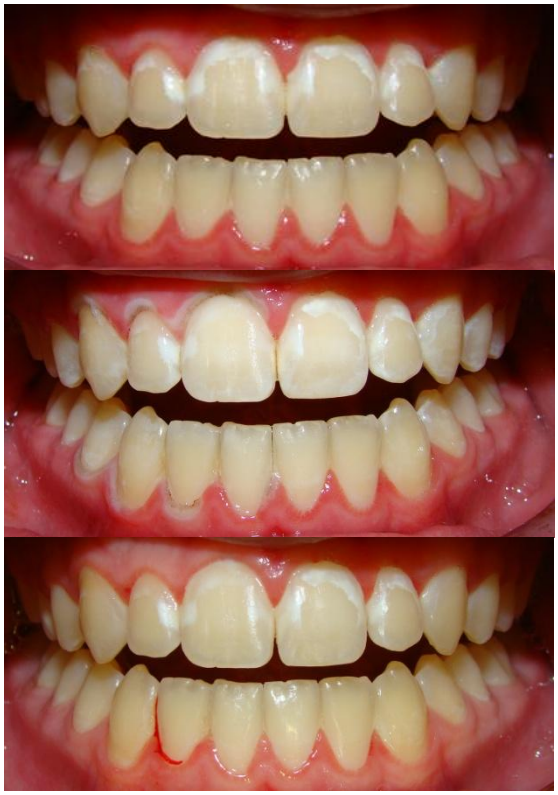

Figure 1. Example of intraoral center photos taken at T1, T2, and T3.

All lesions were scored by a single examiner who was blinded to timepoint and group assignment. A modified Enamel Decalcification Index (EDI), initially developed by Banks and Richmond[86], was used to score each tooth at T1, T2, and T3. This modified EDI scoring system divides each tooth into mesial, distal, gingival, and incisal quadrants and scores quadrants as follows: 0: no lesion present, 1: <25% of quadrant area covered by lesion, 2: 25-50% of quadrant area covered by lesion, 3: 50-75% of quadrant area covered by lesion, and 4: 75-100% of quadrant area covered by lesion (Figure 2).

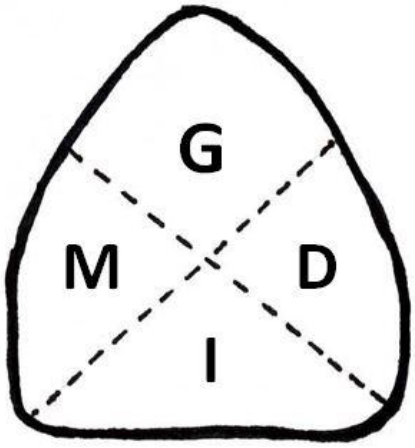

Figure 2. Modified Enamel Decalcification Index. 0: no lesion present, 1: <25% of quadrant area covered by lesion, 2: 25-50% of quadrant area covered by lesion, 3: 50-75% of quadrant area covered by lesion, and 4: 75-100% of quadrant area covered by lesion. M: mesial, G: gingival, D: distal, I: incisal.

Statistical Analysis

Characteristics of study participants (i.e., age, gender, and time out of braces at T1) were described using the median and interquartile range (IQR) or proportions for continuous and categorical variables, respectively. A Kolmogorov-Smirnov test was used to test normality of the outcome (i.e. grade). A Generalized Estimating Equation (GEE) ordinal logistic regression was used to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs) for the association between treatment and lesion grade. The use of GEE allows for the dependence of observations resulting from repeated measurement to be accounted for in statistical models, thus providing more statistically reliable estimates of treatment effect.

The ORs computed from ordinal logistic regression estimate the association between treatment and the probabilities of lesions having a lower ordered grade value.

Models were adjusted for age and time out of braces at the time of treatment. Additionally, to determine whether treatment effect varied by the time out of braces, models were stratified by whether the time out of braces was more than four months (i.e., the median time out of braces). An interaction between treatment and time out of braces was included in a model to determine whether the association between treatment and lesion grade varied by time out of braces.

The proportion of lesion grades between treated and non-treated lesions was compared within time periods (i.e., baseline, post-treatment, follow-up) using a chi-square test. To determine whether the treatment differentially resulted in a change in lesion grade over time, the change in grade was computed for baseline to post-treatment and post-treatment to follow-up. A Wilcoxon ranked sum test was used to determine whether the change in lesions grade was different between treatment groups.

RESULTS

The demographics of study participants are summarized in Table 1. There were a total of 11 participants in the current study, seven males and four females. The median age of participants was 16.5 years with an IQR of 10.4 years. The median time out of braces at initial examination was 0.3 years with an IQR of 9.8 years. Seven of the participants had braces removed within six months of enrollment in the study, while the other 4 participants have been in retention for 7-14 years.

Table 1. Characteristics of 11 individuals treated for lesions after removal of braces

	Median (IQR*) or N (%)
Median age	16.5 (10.4)
Gender	
Male	7 (63.6)
Female	4 (36.4)
Median time out of braces at time of treatment	0.3 (9.8)

* Defined as the difference between the upper and lower quartiles

Table 2 demonstrates the crude and adjusted odds ratios for the association between treatment, lesion grade, and time out of braces. Overall, teeth that were given the treatment were 2.4 times as likely to have lesions graded lower than lesions on teeth without treatment (OR 2.38, 95% CI 1.89-3.00). When adjusted for age and time in which the individual was out of braces, this association became slightly stronger (OR

2.47, 95% CI 1.96-3.10). When stratified by time out of braces, those who were out of braces for more than four months had a slightly stronger association for having a lower grade (OR 2.80, 95% CI 1.98-3.94) than those who were out of braces for no more than four months (OR 2.21, 95% CI 1.62-3.02). The associations by time out of braces, however, were not statistically different (p=0.4482).

Table 2. Crude and adjusted odds ratios* (ORs) and associated 95% confidence intervals for the association between treatment and lesion grade

	cOR (95% CI)	aOR (95% CI)
Overall		
Treatment		
No	Ref	Ref
Yes	2.38 (1.89-3.00)	2.47 (1.96-3.10)†
≤ 4 months out of braces		
Treatment		
No	Ref	Ref
Yes	2.21 (1.62-3.01)	2.21 (1.62-3.02)‡
> 4 months out of braces		
Treatment		
No	Ref	Ref
Yes	2.73 (1.94-3.85)	2.80 (1.98-3.94)‡

* Estimated using GEE ordinal logistic regression models
† Adjusted for age and time out of braces
‡ Adjusted for age

A comparison of lesion grade distribution between treated and non-treated teeth is shown in Table 3. Prior to treatment (T1), there was no difference in the distribution of the lesion grade between the teeth that were and were not to be treated. Specifically, for both groups lesions were equally likely to be graded a 1 or 2 (p=0.0585). At T2, those teeth that were given the treatment were more likely to have a lower grade, with 35.2% of treated teeth given a grade of 0 compared to 9.9% of the non-treated teeth (p<0.0001).

This change in the lesion grade distribution from pre- to post-treatment was significant (p<0.0001). At T3, treated teeth were still more likely to have a lower grade, though the magnitude of the difference in the distribution between treatment groups was not as large (p<0.0001). The change from T2 to T3 was significant (p=0.0004). Overall from T1 to T3, 24% of lesions were completely masked after treatment with Iconl.

Table 3. Comparison of lesion grade distribution between treated and non-treated teeth within and between measurement periods

	Treated	Not treated	p-value	$p\text{-value}_{change}$
Pre-treatment (%)				
0	23.7	22.4	0.0585	-
1	40.4	38.5		
2	26.8	30.2		
3	9.1	7.0		
4	0.0	1.8		
Post-treatment (%)				
0	35.2	9.9	<0.0001	<0.0001
1	40.6	34.6		
2	20.6	39.1		
3	3.6	14.6		
4	0.0	1.8		
Four weeks (%)				
0	47.7	23.4	<0.0001	0.0004
1	36.7	38.0		
2	12.5	30.2		
3	3.1	6.8		
4	0.0	1.6		

* p-value based on chi-square test

† p-value based on Wilcoxon ranked-sum test

Table 4 compares the change in lesion grade between treated and non-treated teeth throughout the study. From T1 to T2, 36.46% of treated lesions decreased by one or more lesion grade compared to only 7.29% of the non-treated lesions (p<0.0001). During

this same time period, 13.28% and 39.06% of treated and non-treated lesions, respectively, increased by one or more lesion grade. From T2 to T3, a further 29.69% of treated lesions and 40.11% of untreated lesions decreased in lesion grade, with only a non-significant amount increasing in grade. Over the course of the study period (i.e. T1-T3), 45.57% of treated lesions decreased in grade compared to 6.25% of non-treated lesions. This difference was statistically significant ($p<0.0001$).

Table 4. Comparison of the change in lesion grade distribution between treated and non-treated teeth within and between measurement periods

	Treated (n=384)	Not treated (n=384)	p-value*
Pre- to Post-treatment (%)			
-3	0.26	0.00	<0.0001
-2	5.47	0.26	
-1	30.73	7.03	
0	50.26	53.65	
1	12.76	34.11	
2	0.52	4.95	
Post-treatment through four weeks (%)			
-3	0.26	0.00	0.0070
-2	3.91	4.95	
-1	25.52	35.16	
0	58.07	53.65	
1	11.98	6.25	
2	0.26	0.00	
Pre-treatment through four weeks (%)			
-3	0.00	0.00	<0.0001
-2	5.47	0.00	
-1	40.10	6.25	
0	53.65	89.84	
1	0.78	3.91	
2	0.00	0.00	

* p-value based on chi-square test

DISCUSSION

Despite efforts to increase oral hygiene practices among orthodontic patients, white spot lesions continue to be a problem associated with orthodontic treatment. Current treatment options range from non-invasive, compliance-driven methods such as fluoride and CPP-ACP to more invasive techniques like microabrasion and restorative treatment. Infiltrant resins such as Icon have recently been introduced as unique treatment options that are minimally invasive yet not reliant on patient compliance. The current study sought to examine the effectiveness of Icon in masking post-orthodontic white spot lesions.

There were a total of 11 participants in the current study accounting for a total of 184 teeth with 499 total graded lesions at T1. Despite the low participant number, the design of the study which relied more on the total number of lesions provided statistically significant results. It was not predicted that there would be a variation between persons regarding treatment result with Icon; nor was it predicted that age or gender would be associated with treatment outcome. Therefore, the strength of the study lies not in the number of participants, but rather, in the total number of lesions available to compare in the treated and untreated control groups.

The current study showed that teeth treated with Icon were more likely to have a lower grade compared to untreated teeth, and this was not significantly affected by time out of braces. Moreover, there was no statistically significant difference in the treatment

effect among participants that had been out of braces for fewer than four months versus those that has been out of braces for a longer period of time. This finding, however, may be skewed due to the small number of participants resulting in a small comparison group for time out of braces. Seven of the participants had only been in retention for seven months at T1, while the other four participants had been out of braces an average of 11.4 years with a range of 7-13 years. It is postulated that the treatment effect of Icon may be affected by lesion age due to the exposure of the lesion to fluoride over time. As postulated by Ogaard, lesions with a continued exposure to fluoride may develop a hypermineralized surface layer with remaining porosity in the body of the lesion.[16] This surface layer may be difficult to penetrate rendering Icon less useful. Thus, further studies investigating the association with lesion age and the effect of Icon should be conducted before making a decision on the ideal time to treat these unaesthetic white spots.

Tables 3 and 4 compare the lesion grades among the treated and untreated groups. Although the grade distribution was similar between groups at T1, the results show that treated lesions were more likely to have a lower grade at T2 and T3 than untreated lesions. There was a reduction in lesion grade in 45.57% of treated lesions compared to only 6.25% of untreated lesions from T1 to T3. This result is comparable to the 31% reduction found by Bailey et al in 2009 after a 12-week daily application of CPP-ACP.[68] Furthermore, 24% of lesions in the treatment group detected at T1 were totally masked at T3. The current study results, however, are significantly less pronounced than the 94% reduction and 61% total masking effect of Icon found by Kim et al in 2011. Although the previous study focused on color change of the lesion in determining the masking effect, it

is clear that the current 45.57% reduction and 24% total masking effect is not comparable to that found by Kim et al.[85]

A transient increase in lesion grade was seen from T1 to T2 among 13.28% and 39.06% of treated and untreated lesions, respectively. At follow up, however, the data shows that most of these lesions either returned to their T1 score or even further reduced in a few instances. This transient increase may be explained by the conditions of treatment. During treatment, all teeth, treated and untreated, were isolated from moisture for at least one hour. Post-treatment pictures were taken immediately following this isolation, which may result in a more pronounced white, opaque appearance of the dehydrated teeth and lesions. Hence, the follow-up pictures taken four weeks after treatment may provide a more accurate representation of the lesion since the teeth were under more normal intraoral conditions at the time of grading.

Overall, this study demonstrated the ability of Icon to successfully reduce lesion size thus improving esthetic appearance. Furthermore, this result appears to be immediate in most cases and stable in the short term. Icon may provide a desirable treatment option for patients wishing to mask post-orthodontic white spot lesions without the hassle of a daily routine that is required by fluoride and CPP-ACP treatment. Unlike fluoride and CPP-ACP, however, Icon is not claimed to remineralize the lesions but rather to fill in the lesion porosity with resin thus restoring the natural optical properties of the tooth. This innovative treatment option may be the best-suited option for many non-compliant patients in which poor oral hygiene has resulted in the unaesthetic appearance of white spots on the facial surface of one or more teeth.

CONCLUSIONS

The following conclusions can be made from the data collected in this study:

1. Icon reduced the size of and completely masked many post-orthodontic white spot lesions *in vivo*.
2. Icon provides an immediate and stable short-term esthetic benefit in masking post-orthodontic white spot lesions *in vivo*.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD FOR HUMAN USE APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on August 29, 2016. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	CRONAN, CANDACE ANN
Co-Investigator(s):	
Protocol Number:	**F110112001**
Protocol Title:	*Clinical Evaluation of Treatment of White Spot Lesions with ICON*

The IRB reviewed and approved the above named project on 1/11/2012. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 1/11/2012

Date IRB Approval Issued: 01-13-12

Identification Number: IRB00000726

Albert Oberman, MD, MPH /db

Albert Oberman, M.D., MPH
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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