Original Article

Esthetic improvements of postorthodontic white-spot lesions treated with resin infiltration and microabrasion: *A split-mouth, randomized clinical trial*

Xi Gu[a]; Lin Yang[b]; Deqin Yang[c]; Yuan Gao[d]; Xiaolei Duan[e]; Xin Zhu[e]; He Yuan[f]; Jiyao Li[g]

ABSTRACT

Objective: To compare the esthetic improvement between postorthodontic white-spot lesions (WSLs) treated by resin infiltration and microabrasion for 12 months.

Materials and Methods: A total of 20 patients with 128 teeth with postorthodontic WSLs were recruited. A simple randomized, split-mouth, positive controlled design was used to allocate patients to resin infiltration or microabrasion groups. The lesion area ratio (R value) was calculated between the area of a WSL and the labial surface of the corresponding tooth based on standardized clinical photographs. The color change (ΔE) of each tooth was measured with a Crystaleye spectrophotometer (Olympus, Tokyo, Japan). Every measurement was taken before treatment (T0) and at different time points after treatment: 1 week (T1), 6 months (T6), and 12 months (T12).

Results: A total of 16 patients with 108 trial teeth were available at T12. Each group had 54 trial teeth. In both groups, there was a significant decrease in R value and ΔE between T1 and T0 ($P < .0001$). In the infiltration group, the R value and ΔE had no significant changes over time from T1 to T12. In the microabrasion group, the R value and ΔE decreased significantly from T1 to T6. The R value of resin infiltration was lower when compared with microabrasion at every recall point ($P < .001$). The ΔE had no significant differences between the two groups at any timepoint.

Conclusions: Resin infiltration and microabrasion improved the esthetic appearance of WSLs and showed sufficient durability for 12 months. Resin infiltration showed a better esthetic improvement effect when compared with microabrasion at 12 months. (*Angle Orthod.* 2019;89:372–377.)

KEY WORDS: Resin infiltration; Microabrasion; White-spot lesions

INTRODUCTION

The development of white spot lesions (WSLs) is one of the most common adverse effects of orthodontic treatment. The formation of WSLs is attributed to the inhibition of adequate oral hygiene by the fixed appliances and the extended period that plaque remains on the teeth.[1] At least 50% of patients with fixed appliances developed one or more WSLs by the end of treatment.[2] In addition, WSLs remain for 5 years

The first two authors contributed equally to this work.

[a] Resident, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China; Resident, Hospital of Stomatology, Hebei Medical University, Shijiazhuang, China.

[b] Attending Doctor, Chongqing Key Laboratory for Oral Diseases and Biomedical Sciences, The Affiliated Hospital of Stomatology, Chongqing Medical University, Chongqing, China.

[c] Professor, Chongqing Key Laboratory for Oral Diseases and Biomedical Sciences, The Affiliated Hospital of Stomatology, Chongqing Medical University, Chongqing, China.

[d] PhD Candidate, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

[e] Resident, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

[f] Attending Doctor, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

[g] Professor, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Department of Operative Dentistry and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

Corresponding author: Dr He Yuan, State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, No. 14, Section 3, Renmin Road South, Chengdu, Sichuan 610041, China
(e-mail: yuanhe-06@163.com)

Accepted: December 2018. Submitted: April 2018.
Published Online: February 5, 2019

after appliance removal, indicating the impending need for treatment.[3] The enamel demineralization remains a challenge in orthodontics, and the presence of WSLs significantly affects the esthetic appearance of the teeth and quality of life. Several studies have shown that the use of fluoride or casein phosphopeptide-amorphous calcium phosphate may regress WSLs.[4,5] However, the surface hypermineralization formed by the use of high concentrations of fluoride may arrest remineralization and increase the risk of permanent brown organic staining, which might endanger the esthetic treatment result.[6]

Resin infiltration, developed recently, aims to arrest caries lesion progression by the penetration of low-viscosity resin into the enamel.[7] The infiltrated resin forms a diffusion barrier on the enamel surface and within the enamel, thus blocking the entry for acid.[8] Resin infiltration has been shown to have a positive effect in improving the appearance of WSLs, making the lesions look similar to sound enamel.[9–12]

It was reported that microabrasion could improve the appearance of teeth by eliminating the outer defective layer of the enamel.[13] Clinical studies have confirmed the benefit of using microabrasion to obtain a good esthetic outcome for WSLs.[14,15] The components of microabrasion include 6.6% hydrochloric acid and 20- to 160-μm-sized silicon carbide microparticles that removes superficial parts of a lesion by chemical erosion and mechanical abrasion.[16]

One case report comparing the esthetic effect of resin infiltration and microabrasion for WSLs showed that the resin infiltration technique seemed more efficient, with a diminution of lesion size.[16] However, the long-term esthetic improvement of resin infiltration or microabrasion for WSLs is still unknown. It is very difficult for clinicians to determine which method is better for treating WSLs. There is still a lack of reliable evidence that could support camouflaging strategies to manage postorthodontic WSLs based on a recent systematic review.[6]

The purposes of this 1-year follow-up study were (1) to assess the esthetic improvements for postorthodontic WSLs treated with resin infiltration or microabrasion using clinical photographs and spectrophotometry and (2) to compare the esthetic improvement between these two techniques used to treat WSLs. The hypothesis was that resin infiltration and microabrasion were both effective in esthetic improvement of WSLs but that resin infiltration would show greater esthetic improvement.

MATERIALS AND METHODS

Patients and Interventions

The study design was a single-center, split-mouth, positive-controlled simple randomized clinical trial in which patients were treated with resin infiltration or microabrasion. The patients were recruited from the West China Hospital of Stomatology, Sichuan University (Chengdu, China).

Inclusion criteria were patients aged 12 to 19 years who had finished fixed orthodontic treatment with debonding more than 3 months previously with the presence of WSLs induced by brackets on the anterior teeth (International Caries Detection and Assessment System II ICDAS-II code 2[17]). The exclusion criteria were cavitated lesions, as well as resin composites, veneers, crowns, and the presence of any developmental enamel defects, such as enamel hypoplasia, fluorosis, and tetracycline staining on anterior teeth.

A signed informed consent was obtained from every participant or their guardians. Ethical approval was given by the medical ethics committee at West China Hospital of Stomatology, Sichuan University (WCHSIRB-ST-2013-97) prior to the study. The study was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-16009908).

A total of 20 patients were recruited with a total of 128 anterior maxillary or mandibular teeth with WSLs. Resin infiltration was performed on either the right or left sides of the maxillary or mandibular anterior teeth on the basis of random allocation, with the other side treated by microabrasion. Simple randomized quadrant allocation (Preparing opaque envelopes containing different quadrant treatment assignments, one quadrant as resin infiltration, the other as microabrasion) was performed by lots before the trial by one clinician who was not responsible for treatment. Allocations were concealed in opaque envelopes by a person who was not involved in the trial. Each group had 64 trial teeth. According to the manufacturers' instruction, infiltration (Icon, DMG, Hamburg, Germany) or microabrasion (Opalustre Enamel Microabrasion Slurry, Ultradent, South Jordan, Utah, USA) was applied to WSLs. Briefly, in the infiltration group, the etching (Icon-Etch, DMG) and drying steps (Icon-Dry, DMG) could be repeated two or three times in cases of engrained lesions through visual assessment after each etch/dry interval. Then, the infiltrant was applied to the lesions twice. In the microabrasion group, abrasive material was applied on the surface of the teeth and mechanical friction was performed with a rubber cup at 500 r/min speed, lasting 30 to 40 seconds. The material was then rinsed with water spray. This procedure was repeated up to 10 times.

Standardized Intraoral Photographs

Measurements were conducted before treatment (T0) and 1 week after (T1), 6 months after (T6), and 12 months after (T12) treatment. All of the intraoral photographs were taken under the same conditions.

Intraoral photographs were taken using a digital camera (EOS 500D camera, Canon, Tokyo, Japan), macro lens (MACRO LENS EF 100 mm, Canon), and circular flash (MACRO RING LITE, MR-14EX, Canon). The camera settings were as follows: shutter speed 1/200, F29, ISO 400, and auto white balance. The images were analyzed by Photoshop CS3 software (Adobe Systems Incorporated, San Jose, California, USA). Demineralized WSLs and total area of the labial surface of the tooth were outlined on the same computer screen by the investigator (Figure 1). All examinations were performed by the same investigator, and the photographs were randomly labeled to avoid unwanted bias. Area ratio (R value) was calculated as the area ratio of WSLs to the labial surface:

$$\text{R value} = \frac{\text{area of lesions}}{\text{area of the labial surface of the tooth}} * 100\%$$

Crystaleye Spectrophotometer

The enamel color of the tooth surface was measured using the Crystaleye spectrophotometer (Olympus, Tokyo, Japan). All measurements were performed with the patients' lips closed to exclude the distortive variation of ambient light. Images were captured for each tooth and analyzed with the Crystaleye software (version 1.4, Olympus). The assessment field was captured using system target caption, and the locations of the assessment field outlines were restored to assess the retrieval of the masked WSLs and sound adjacent enamel in the follow-ups. Color and lightness characteristics (L^* a^* b^*) of the respective WSLs and sound adjacent enamel assessment areas were recorded. Color change between the treated lesions and the adjacent sound enamel was expressed as ΔE values: $\Delta E = (\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2})^{(1/2)}$.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 19.0, SPSS Inc., Chicago, Illinois, USA). The mean R value and ΔE were calculated for each group. Multifactorial analysis of variance with repeated measures and pairwise comparisons were used to analyze the data. In all tests, a 5% significance level was adopted.

Method Error Assessment

To determine the intraobserver reliability of the measurements, 10 teeth were evaluated by the same operator in vivo 1 week after the first assessment. The reproducibility of the measurements was tested by intraclass correlation coefficient. The intraclass correlation coefficients were 0.95 for L^* value, 0.97 for a^* value, 0.97 for b^* value, and 0.91 for R value analysis.

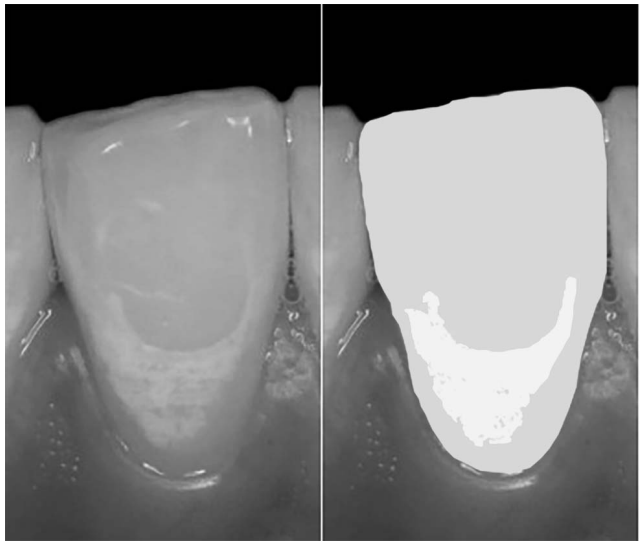

Figure 1. Photographic analysis: mandibular right incisor showing areas of measurement obtained in Photoshop CS3 (Adobe Systems Incorporated, San Jose, California, USA). Gray, area of the labial surface; white, the area of lesions.

RESULTS

A total of 20 patients (12 female, 8 male; mean age 16 years) with 128 teeth (78 maxillary teeth, 50 mandibular teeth) participated in the study. A total of 16 participants (9 female, 7 male; mean age 15.5 years) with 108 teeth (n = 54 per group; 66 maxillary teeth, 42 mandibular teeth) were available at T12. Of the participants, 4 were lost during the trial.

At baseline (T0), the R value and ΔE in the two groups did not differ significantly (Tables 1 and 2). R value decreased significantly after both treatments ($P < .0001$; Table 1 and Figure 2). In the infiltration group, the R value decreased from T1 (5.85%) to T6 (4.31%), but the difference was not significant ($P = .0549$). The R value in the infiltration group did not show significant differences among the recall timepoints. In the microabrasion group, the R value decreased significantly from T1 to T6 ($P < .0001$) and from T6 to T12 ($P = .0313$). The R value in the infiltration group was lower when compared with the microabrasion group regardless of the time after treatment ($P < .001$).

As shown in Table 2 and Figure 3, ΔE decreased significantly at T1 in both groups. There was no significant change from 1 week to 12 months in the infiltration group. In the microabrasion group, there was a significant difference between T1 and T6 ($P = .0003$), but there was no significant difference between T6 and

Table 1. R Value (Percentage ± Standard Deviation) of the Two Treatments at T0, T1, T6, and T12, Along With *P* Values

	Time				*P* Value			
Group	T0	T1	T6	T12	T0 vs T1	T1 vs T6	T1 vs T12	T6 vs T12
Infiltration	36.13 ± 9.94	5.85 ± 4.84	4.31 ± 3.34	4.32 ± 3.69	<.0001	.0549	.0999	.9911
Microabrasion	34.03 ± 13.66	17.39 ± 11.9	12.82 ± 10.65	10.99 ± 9.53	<.0001	<.0001	<.0001	.0313
P value	.5194	<.0001	.0002	.0013				

T0: before treatment; T1: 1 week after treatment; T6: 6 months after treatment; T12: 12 months after treatment.

T12 ($P = .0996$). At all timepoints, ΔE did not show a significant difference between the two groups.

DISCUSSION

This study investigated the long-term esthetic effect of resin infiltration. The R value was reduced by 30% after infiltration treatment, showing a reduction in lesion area. $\Delta E < 3.7$ is considered to be a clinically acceptable color difference.[18] In this study, the ΔE value after treatment was 2.21 ± 0.99, indicating that the infiltrated lesions had a clinically acceptable color recovery. This result was consistent with earlier reports of clinical trials,[10-12,19] case reports,[9] and in vitro research.[20] The color recovery is attributed to the similar refractive index of sound enamel (refractive index = 1.62) and the infiltrant (refractive index = 1.52).[9] With respect to R value and ΔE value changes over time, no significant changes were observed at recall timepoints, indicating that the effect of resin infiltration on reducing lesion area and returning enamel to a natural color was stable during a period of 12 months. The result corresponded with a clinical trial that reported the color and lightness characteristics of the Icon infiltrant were not altered significantly after 12 months.[12]

Esthetic changes induced by microabrasion to WSLs included reduction of the size of the lesion by 17% and significant reduction of the ΔE value after treatment, indicating that microabrasion could reduce the lesion area and improve the color appearance. This finding was supported by another study advocating microabrasion for the removal of WSLs.[5,15] The esthetic improvement of WSLs by microabrasion is the result of the removal of the superficial part of lesions by chemical erosion with hydrochloric acid and mechanical abrasion with pumice, resulting in the smoothness and glossiness of the lesion.[21] The R value at T1 was significantly different than that at T6, showing that the treated lesions had a further lesion area reduction over time. This may be attributed to remineralization of inner demineralized areas exposed by removal of the superficial part of lesions. The outer 10 to 30 μm of the WSLs was considered to be relatively intact enamel because of the supersaturation of fluorapatite.[22] Previous investigators reported that microabrasion could remove 250 μm of superficial enamel.[15] Thus, microabrasion could remove the relatively intact outer and inner layers of WSLs, resulting in the direct contact of lesions with saliva for remineralization. After treatment, there was a significant difference in ΔE between T1 and T6 ($P = .0003$), but no significant difference between T6 and T12 ($P = .0996$), indicating that microabrasion treatment could improve WSLs relative to the surrounding enamel and that the color recovery in 6 months was stable at 12 months.

This study also compared the effects between infiltration and microabrasion. The R value of resin infiltration was lower when compared with microabrasion at all recall points, indicating that the resin infiltration was more effective in decreasing lesion size when compared with microabrasion. A case report also demonstrated that the resin infiltration technique was more effective than microabrasion in reducing lesions.[16] No significant difference in ΔE was observed between the two groups. This result showed that the 12-month color effect of the two treatments was not different. The possible reason for this was that the WSL field captured using the Crystaleye spectrophotometer was the small central part of the lesion, whereas the residual WSL of treated teeth was often observed on the margin of the lesion. The power of the test between the groups' ΔE value was 6.5%. The possible reason for the low power was that the difference between the groups was too small to detect the difference.

Table 2. Color Change Value (Mean ± Standard Deviation) at T0, T1, T6, and T12 of the Two Treatments, Along With *P* Values

	Time				*P* Value			
Group	T0	T1	T6	T12	T0 vs T1	T1 vs T6	T1 vs T12	T6 vs T12
Infiltration	6.57 ± 2.48	2.21 ± 0.99	2.20 ± 0.82	2.03 ± 0.82	<.0001	.9285	.1704	.1249
Microabrasion	5.62 ± 2.04	2.66 ± 1.02	2.26 ± 0.93	2.08 ± 1.06	<.0001	.0003	<.0001	.0996
P value	.1291	.1034	.7941	.8470				

T0: before treatment; T1: 1 week after treatment; T6: 6 months after treatment; T12: 12 months after treatment.

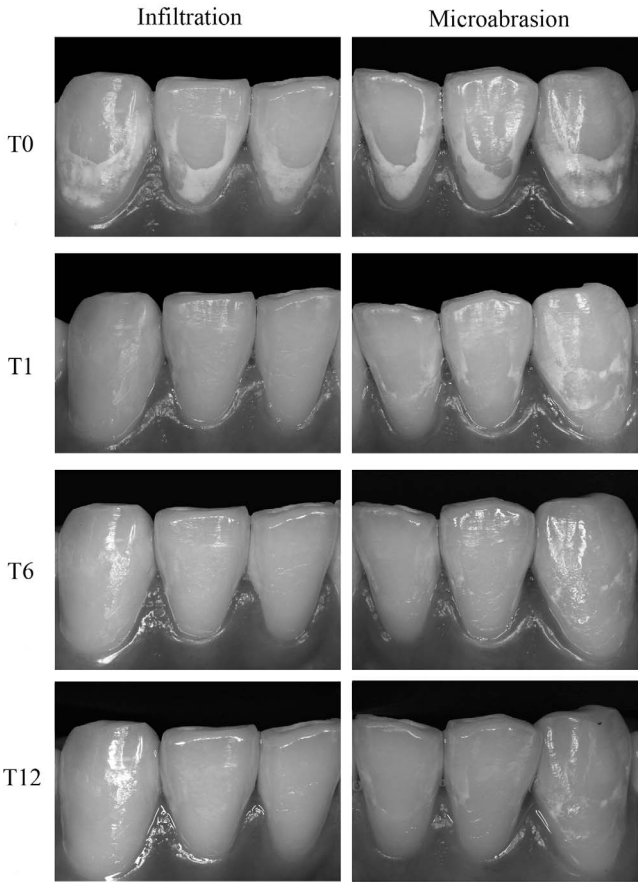

Figure 2. Representative photographs of a patient treated with resin infiltration and microabrasion recorded with a digital camera during the 12-month follow-up period.

Unfortunately, neither resin infiltration nor microabrasion could remove the lesions completely. The reason might be related to the depth of the lesions. Previous investigators reported that microabrasion could remove 250 μm of superficial enamel.[15] The penetration depth of resin infiltration could be more than 100 μm.[23] If the depth of the WSLs was deeper than the maximum depth of the treatment technique, the lesions could not be removed completely. A method for clinically detecting the depth of WSLs is needed to distinguish the indications of the two techniques. Torlakovic et al.[24] reported a significant correlation between WSL color intensity and lesion volume, indicating that WSL color intensity might predict the depth of enamel demineralization.

Of the 16 participants, 1 at T12 was observed to have staining on the treated tooth. The oral hygiene of this patient was inadequate. The patient had the habit of consuming beverages containing yellow pigment in the previous 6 months. After a careful check, the staining was mainly located at the cervical, mesial, and distal margins, and some new WSLs could be seen at

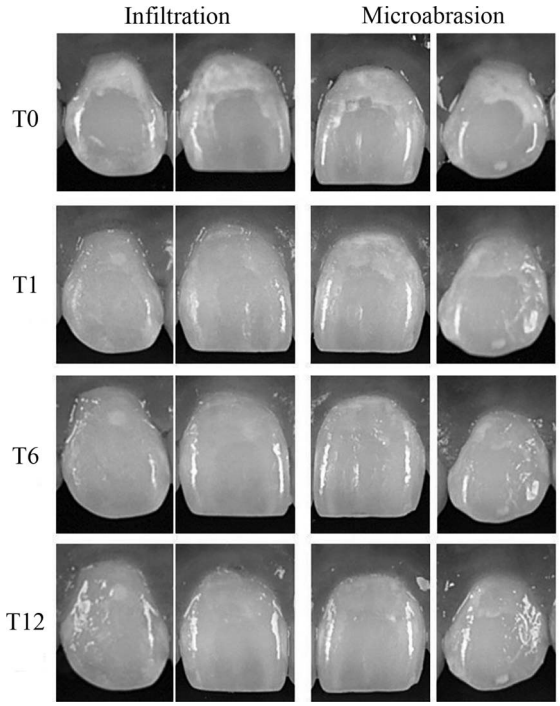

Figure 3. Representative pictures of a patient treated with resin infiltration and microabrasion recorded with Crystaleye spectrophotometer (Olympus, Tokyo, Japan) during a period of 12 months.

the cervical part of enamel surfaces. The possible reasons for staining included (1) consuming drinks with yellow pigment staining the treated lesions, (2) the margins could not be easily cleaned when brushing the teeth, (3) the margins could not be easily reached when polishing after infiltration or using the rubber cup for microabrasion. The new WSLs might have resulted from the accumulation of plaque at these areas. This case served as a reminder that the possibility of staining exists after the resin infiltration or microabrasion. Therefore, more than 12 months of follow-up may be needed to identify the long-term effects of resin infiltration and microabrasion.

It was reported that some WSLs disappeared within several weeks, and most lesions decreased within 3 months.[25] Kim et al.[10] suggested that resin infiltration treatment should be applied more than 3 months after debonding. So in the present study, patients were selected only with debonding times greater than 3 months.

The present study was a randomized split-mouth study, which created divisions within the mouths of patients that were randomly assigned to treatments.[26] In this split-mouth study, the patients acted as their own controls, which could boost the power of the study and eliminate intersubject variability when compared with a design of a patient and his or her whole mouth being assigned to one treatment.[27] Fewer participants were needed to estimate the treatment effect because of the increased statistical efficiency.[26] However, the

split-mouth design may carry a risk of biased treatment efficacy because of a possible carry-across effect.[27] In this study, contamination of the effects of resin infiltration to microabrasion did not pose a problem because of the operating methods of these two treatment techniques.

CONCLUSIONS

- In the 12-month observation period, resin infiltration had an immediate and long-term esthetic improvement of postorthodontic WSLs that was stable, whereas microabrasion showed significant improvement during the follow-up period.
- After the 12-month follow-up, resin infiltration seems to be still more effective for esthetic improvement of WSLs when compared with microabrasion.

ACKNOWLEDGMENTS

This work was supported by the Science and Technology Benefiting Project of Chengdu (Grant 2014-HM02-00041-SF) and by the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (Grant 20911BAZ03171).

REFERENCES

1. Sakamaki ST, Bahn AN. Effect of orthodontic banding on localized oral lactobacilli. *J Dent Res*. 1968;47:275–279.
2. Gorelick L, Geiger AM, Gwinnett AJ. Incidence of white spot formation after bonding and banding. *Am J Orthod*. 1982;81: 93–98.
3. Ogaard B. Prevalence of white spot lesion in 19-years-old: a study on untreated and orthodontically treated persons 5 years after treatment. *Am J Orthod Dentofacial Orthop*. 1989;96:423–427.
4. Agarwal A, Pandey H, Pandey L, et al. Effect of fluoridated toothpaste on white spot lesions in postorthodontic patients. *Int J Clin Pediatr Dent*. 2013;6:85–88.
5. Akin M, Basciftci F. Can white spot lesions be treated effectively? *Angle Orthod*. 2012;82:770–775.
6. Sonesson M, Bergstrand F, Gizani S, et al. Management of post-orthodontic white spot lesions: an updated systematic review. *Eur J Orthod*. 2017;39:116–121.
7. Meyer-Lueckel H, Paris S. Progression of artificial enamel caries lesions after infiltration with experimental light curing resins. *Caries Res*. 2008;42:117–124.
8. Paris S, Meyer-Lueckel H, Kielbassa AM. Resin infiltration of natural caries lesions. *J Dent Res*. 2007;86:662–666.
9. Paris S, Meyer-Lueckel H. Masking of labial enamel white spot lesions by resin infiltration—a clinical report. *Quintessence Int*. 2009;40:713–718.
10. Kim S, Kim EY, Jeong TS, Kim JW. The evaluation of resin infiltration for masking labial enamel white spot lesions. *Int J Paediatr Dent*. 2011;21:241–248.
11. Hammad SM, El Banna M, El Zayat I, Mohsen MA. Effect of resin infiltration on white spot lesions after debonding orthodontic brackets. *Am J Dent*. 2012;25:3–8.
12. Eckstein A, Helms HJ, Knösel M. Camouflage effects following resin infiltration of postorthodontic white-spot lesions in vivo: one-year follow-up. *Angle Orthod*. 2015;85: 374–380.
13. Benbachir N, Ardu S, Krejci I. Indications and limits of the microabrasion technique. *Quintessence Int*. 2007;38:811–815.
14. Souza de Barros Vasconcelos MQ, Almeida Vieira K, da Consolação Canuto Salgueiro M, et al. Microabrasion: a treatment option for white spots. *J Clin Pediatr Dent*. 2014; 39:27–29.
15. Murphy TC, Willmot DR, Rodd HD. Management of postorthodontic demineralized white lesions with microabrasion: a quantitative assessment. *Am J Orthod Dentofacial Orthop*. 2007;131:27–33.
16. Son JH, Hur B, Kim HC, Park JK. Management of white spots: resin infiltration technique and microabrasion. *J Korean Acad Conserv Dent*. 2011;36:66–71.
17. Ismail Ai, Sohn W, Tellez M, et al. The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. *Community Dent Oral Epidemiol*. 2007;35:170–178.
18. Johnston WM, Kao EC. Assessment of appearance match by visual observation and clinical colorimetry. *J Dent Res*. 1989;68:819–822.
19. Knösel M, Eckstein A, Helms HJ. Durability of esthetic improvement following Icon resin infiltration of multibracket-induced white spot lesions compared with no therapy over 6 months: a single-center, split-mouth, randomized clinical trial. *Am J Orthod Dentofacial Orthop*. 2013;144:86–96.
20. Yuan H, Li J, Chen L, et al. Esthetic comparison of white-spot lesion treatment modalities using spectrometry and fluorescence. *Angle Orthod*. 2014;84:343–349.
21. Ardu S, Castioni NV, Benbachir N, Krejci I. Minimally invasive treatment of white spot enamel lesions. *Quintessence Int*. 2007;38:633–636.
22. Larsen MJ. Chemical events during tooth dissolution. *J Dent Res*. 1990;69:575–580.
23. Kielbassa AM, Muller J, Gernhardt CR. Closing the gap between oral hygiene and minimally invasive dentistry: a review on the resin infiltration technique of incipient (proximal) enamel lesions. *Quintessence Int*. 2009;40:663–681.
24. Torlakovic L, Olsen I, Petzold C, et al. Clinical color intensity of white spot lesions might be a better predictor of enamel demineralization depth than traditional clinical grading. *Am J Orthod Dentofacial Orthop*. 2012;142:191–198.
25. Artun J, Thylstrup A. A 3-year clinical and SEM study of surface changes of carious enamel lesions after inactivation. *Am J Orthod Dentofacial Orthop*. 1989;95:327–333.
26. Lesaffre E, Garcia Zattera M, Redmond C, et al. Reported methodological quality of split-mouth studies. *J Clin Periodontol*. 2007;34:756–761.
27. Lesaffre E, Philstrom B, Needleman I, et al. The design and analysis of split-mouth studies: what statisticians and clinicians should know. *Stat Med*. 2009;28:3470–3482.