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ORIGINAL RESEARCH

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Resin infiltration versus self-assembling peptide P11-4 with and without fluoride varnish for white spot lesions in children: a randomized controlled trial

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Abstract

Background: Comparative clinical evidence regarding minimally invasive protocols for non-cavitated white spot lesions (WSLs) in children remains limited. This trial compared resin infiltration (RI), self-assembling peptide P11-4 monotherapy, and P11-4 with 5% sodium fluoride varnish (P11-4 + FV) over 6 months. **Methods**: In this multicenter, single-masked, three-arm parallel randomized controlled trial, 105 children aged 7–14 years with non-cavitated WSLs (International Caries Detection and Assessment System (ICDAS II) score 2) on both maxillary central incisors were randomized at the patient level (35 per group; 210 teeth). The primary outcome was color change (ΔE), assessed using CIE L*a*b* (CIELAB) photographic analysis; secondary outcomes were visual lesion regression (ICDAS II) and lesion activity measured using DIAGNOdent. Given baseline imbalance, prespecified baseline-adjusted analyses (linear mixed-effects models, analysis of covariance (ANCOVA), and rank-based ANCOVA) informed primary inference. Significance was set at $p < 0.05$. **Results**: Two hundred teeth were analyzed per protocol. After adjusting for baseline severity, between-group differences in color change were not significant ($p = 0.094$). RI produced the most rapid ICDAS II improvement (score 1.32, standard deviation (SD) 0.94, post-treatment). Because DIAGNOdent readings from infiltrated surfaces are confounded by the resin optical pathway, fluorescence comparisons were restricted to non-resin arms; at 6 months, P11-4 + FV was lower (mean 1.10, SD 0.94) than P11-4 monotherapy (mean 3.79, SD 3.26; $p < 0.001$), which showed a significant rebound. **Conclusions**: No significant between-group difference in color outcome remained after baseline adjustment; as the trial was not powered for equivalence, this reflects a non-detected rather than proven difference. RI provided the most rapid visual improvement, whereas P11-4 + FV showed the most durable reduction in lesion-activity fluorescence. Protocol selection should follow the primary goal: rapid esthetic correction (RI) or durable lesion-activity control (P11-4 + FV). **Clinical Trial Registration**: ClinicalTrials.gov NCT06708481 (prospectively registered, August 2024).

Keywords

White spot lesion; Resin infiltration; Self-assembling peptide P11-4; Fluoride varnish; Randomized controlled trial; Remineralization

1. Introduction

White spot lesions (WSLs) represent the earliest clinically detectable sign of enamel demineralization and are highly prevalent among children and adolescents [1]. Healthy enamel comprises approximately 96% inorganic material (primarily hydroxyapatite, with a refractive index of 1.62), along with a minor organic matrix and water. Conversely, the hypomineralized enamel of WSLs contains air (refractive index 1.0) and organic fluid (1.33), which increase light scattering and produce the characteristic chalky appearance [2]. Non-orthodontic, developmental WSLs on permanent maxillary incisors represent one of the most common esthetic and minimally invasive treatment challenges in pediatric dentistry. Despite their high prevalence in school-aged children, comparative evidence to guide treatment protocol selection for this demographic remains limited, as most existing clinical trials have focused on post-orthodontic lesions.

Currently, three minimally invasive interventions are widely used in clinical practice. Resin infiltration (RI), introduced in 2009, employs a low-viscosity resin (refractive index 1.52) that fills enamel porosities, acts as a diffusion barrier, and optically masks the lesion [3]. Alternatively,

the self-assembling peptide P11-4 (CURODONT REPAIR; Credentis AG, Windisch, Switzerland) diffuses into the lesion, forming a three-dimensional scaffold that promotes *de novo* hydroxyapatite formation [4]. Furthermore, combining P11-4 with 5% sodium fluoride varnish (P11-4 + FV) is hypothesized to exert a synergistic effect: fluoride provides an optimal ionic environment for surface remineralization, while the peptide scaffold drives subsurface mineral nucleation [5].

Although *in vitro* evidence supports each approach, head-to-head clinical comparisons remain sparse. In a pH-cycling study, Wierichs *et al*. [6] reported that under demineralizing conditions, P11-4 monotherapy neither inhibited lesion progression nor masked lesion appearance; in contrast, RI provided effective optical masking, and the combination of P11-4 with fluoride demonstrated an additive effect on mineral retention. Subsequent randomized clinical trials involving pediatric and adolescent cohorts treated with P11-4 and fluoride have reported sustained improvements in lesion appearance and activity over 6–12 months [7, 8]. However, to our knowledge, no published clinical trial has directly compared RI, P11-4 monotherapy, and P11-4 + FV in children within a single protocol, using parallel esthetic, visual, and fluorescence outcomes. Addressing this gap is clinically critical for several reasons. First, the newly erupted permanent incisors of young children feature incompletely matured enamel, and therefore their remineralization kinetics may differ significantly from those of adult or post-orthodontic populations. Second, the multi-step RI protocol demands prolonged isolation and patient cooperation, presenting challenges for young or anxious children; therefore, the shorter chair time associated with P11-4-based protocols may offer a distinct practical advantage. Third, because WSL management in children is frequently integrated into a long-term caries prevention strategy for the developing dentition, the durability of subsurface remineralization is considered as clinically relevant as the immediate esthetic outcome.

Consequently, this trial aimed to compare color change, quantified by ΔE (primary outcome), as well as visual lesion regression via ICDAS II and lesion-activity fluorescence measured using DIAGNOdent (secondary outcomes). These parameters were evaluated across the RI, P11-4 monotherapy, and P11-4 + FV intervention groups over 6-month follow-up period in children presenting with non-cavitated WSLs on their maxillary permanent central incisors. Additionally, caries arrest was assessed as a surrogate secondary outcome, inferred from the combined trajectories of the ICDAS II scores and DIAGNOdent measurements.

2. Materials and methods

2.1 Study design and ethics

This multicenter, single-masked, three-arm parallel randomized controlled trial was conducted at two university pediatric dentistry clinics between August and November 2024. Recruitment and active treatment were completed within this timeframe, and follow-up assessments were conducted approximately six months after each participant's initial treatment visit. The trial was prospectively registered (ClinicalTrials.gov NCT06708481) and is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. Prior to enrollment, ethics approval was obtained from the Research Ethics Committee of the Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt (initial approval code: P-PD-24-02, 2024), and from the Research Ethics Committee of the Faculty of Dentistry, October 6 University, Giza, Egypt (approval code: RECO6U/6-2024, 04 March 2024). Following study completion, final approval for documentation and publication was granted by the Al-Azhar committee in 2025 (final approval code: REC-PD-25-01). All procedures were conducted in accordance with the ethical standards of the responsible institutional review committees and the 2013 revision of the Declaration of Helsinki (2013 revision). Written informed consent for both participation and publication was obtained from parents or legal guardians; additionally, children aged 7 years and older provided written assent.

2.2 Participants

Eligible participants included children aged 7–14 years presenting with non-cavitated WSLs on the smooth labial surfaces of both maxillary permanent central incisors (Fédération Dentaire Internationale (FDI) notation: 11 and 21). These lesions were required to be of comparable size, opacity, and overall appearance. Furthermore, eligibility necessitated that the labial surfaces of both incisors be fully erupted, providing full access to the complete clinical crown for standardized photographic capture, ICDAS II scoring, and DIAGNOdent measurement. Additional inclusion criteria were: ICDAS II score 2; vital pulp status; absence of systemic disease affecting home oral care; maintenance of reinforced daily oral hygiene; and informed consent. Exclusion criteria were: periodontal disorder or radiographically detected periapical pathology; existing restorations on the target teeth; and any previous or planned WSL interventions. At enrolment, all participants and their caregivers received standardized oral-hygiene instructions. This regimen comprised twice-daily toothbrushing with a fluoridated toothpaste using an age-appropriate technique, supplemented by dietary counseling to limit the frequency of consumption of sugar-containing and acidic food and beverages. These instructions were reinforced consistently at every subsequent visit.

2.3 Sample size

The tooth served as the pre-specified unit of analysis. Based on findings by Gholami *et al*. [9], who reported a mean (SD) color change of 4.39 (2.5) in an RI group, and assuming a minimal clinically meaningful between-group difference of 1.5 ΔE units, an alpha level of 0.05 (two-sided), and a statistical power of 0.90, the minimum required sample was calculated as 59 teeth per group (G*Power 3.1.9.7; Heinrich-Heine-Universität, Düsseldorf, NRW, Germany) [10]. To account for an anticipated 20% attrition rate, this target was initially inflated to 71 teeth per group, with exactly 70 teeth per group ultimately randomized. Because the study protocol dictated that each child would contribute two eligible incisors, a total of 35 children per group (total sample size n = 105) were

enrolled.

2.4 Randomization, allocation concealment and blinding

Patient-level randomization was generated using a computerized sequence (RANDOM.ORG; Randomness and Integrity Services, Dublin, Ireland). Group allocation was securely concealed within sequentially numbered, opaque, sealed envelopes, which were opened chairside immediately before treatment. To ensure complete and ethical treatment provision, all eligible WSLs within a single patient received the identical allocated protocol; consequently, both eligible teeth in each child were assigned to the same treatment group. The outcome assessors and the photographic image analyst remained masked throughout the follow-up period. However, owing to the visually distinct nature of the clinical application procedures, the operating clinicians were not blinded.

2.5 Outcome measures

The primary outcome was color change quantified by ΔE, derived from standardized CIELAB photographic analysis, with digital photography serving as the primary measurement instrument, and ΔE as the outcome measure. Secondary outcomes included visual lesion regression, evaluated using ICDAS II scores, and lesion activity/subsurface fluorescence by DIAGNOdent pen readings (KaVo, Biberach, Germany), a diagnostic instrument previously validated for caries detection and assessment in children [11]. All three outcomes were collected at baseline, immediately post-treatment, and at the 6-month follow-up. These measures successfully capture different facets of lesion behavior: ΔE reflects color change; ICDAS II reflects visual lesion-stage regression; and DIAGNOdent reflects fluorescence-based lesion activity. For RI, post-treatment changes in ΔE and DIAGNOdent reflect a combined effect of optical masking by the resin layer and any subsequent biological changes. Conversely, for P11-4 and P11-4 + FV, these metrics primarily reflect biological remineralization. A prospective methodological caveat was specifically established for the DIAGNOdent outcome: because the infiltrant resin physically alters the optical pathway of the laser-induced fluorescence, the post-treatment reduction in DIAGNOdent readings for the RI group represents, in part, an optical artifact rather than a pure index of remineralization. Consequently, cross-group DIAGNOdent comparisons involving the RI arm were interpreted with caution, and biologically meaningful fluorescence comparisons were strictly restricted to the two non-resin arms (P11-4 and P11-4 + FV).

2.6 Standardized intraoral photography and ΔE analysis

Photographic documentation was performed using a Canon EOS 1100D digital single-lens reflex (DSLR) camera equipped with a Canon 100 mm macro lens (1:1 magnification) and a TT 560 ring flash with a softbox diffuser (Canon, Tokyo, Japan). All images were acquired in the same dental surgery under controlled ambient lighting conditions (dental chair light off; room illumination fixed at approximately 500 lux). A custom white-balance card (ColorChecker White Balance; X-Rite, Grand Rapids, MI, USA) was photographed at the beginning of each session to establish an in-camera custom white-balance preset. Additionally, a polarizing filter attached to the ring flash was used to suppress specular highlights. For each participant, all images were captured during the same session segment using identical manual camera settings (M mode, f/20, 1/125 s, ISO 100, manual focus), stabilized by a fixed lip-retractor and a standardized camera-to-tooth distance jig. The resulting RAW image files were processed in Lightroom Classic (13.3 and 14, Adobe Inc., San Jose, CA, USA) using a single, unified custom white-balance profile across all visits, before being exported as uncompressed Tagged Image File Format (TIFF) files for CIELAB analysis. ΔE was calculated as $\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$ between the WSL region of interest and an area of sound region on the same tooth. The region of interest for this calculation was defined as the most opaque area of each lesion, which was subsequently compared against a reference measurement taken from adjacent, clinically sound enamel on the same tooth. All photographic captures and subsequent CIELAB coordinate measurements were performed by a single operator, who was blinded to both the treatment group and assessment time point. Intra-examiner repeatability was assessed by re-analyzing 20% of randomly selected photographs, which demonstrated excellent agreement (two-way mixed-effects, absolute-agreement, single-measure intraclass correlation coefficient (ICC), ICC(A,1) = 0.95).

2.7 Clinical procedures

Each tooth was cleaned with a non-fluoridated prophylaxis paste and air-dried for 5 s. The teeth were then examined under a dental light by two calibrated examiners (consensus resolved disagreements) and assessed by ICDAS II and DIAGNOdent (Probe B; KaVo, Biberach, BW, Germany) following manufacturer-recommended calibration protocols against a ceramic reference standard and a sound-enamel zero baseline.

Group RI: Following isolation and polishing, a 15% hydrochloric acid gel (ICON-Etch) was applied for 2 min and subsequently rinsed for 30 s. The surface was desiccated using ethanol (ICON-Dry) for 30 s. The ICON-Infiltrate resin was then applied and left for 3 min; excess material was removed, and the resin was light-cured for 40 s (Elipar; 3M ESPE, St Paul, MN, USA). A second infiltration cycle was then performed following the same protocol.

Group P11-4: A 2% sodium hypochlorite solution was applied for 20 s, followed immediately by 35–37% phosphoric acid for 20 s. The enamel surface was thoroughly rinsed and dried. CURODONT REPAIR was applied, allowed to diffuse into the lesion for 5 min, and air-dried.

Group P11-4 + FV: The initial protocol mirrored that of Group P11-4. Following the diffusion and drying of the peptide, a single application of 5% sodium fluoride varnish (Profluorid Varnish) was applied and allowed to dry for 2 min. No supplementary fluoride varnish applications were performed during the follow-up period.

Post-treatment, parents were instructed to withhold food and beverages for 45 min (P11-4 and P11-4 + FV groups only), to avoid hot liquids for 2 h, and restrict the child's diet

to soft foods for the rest of the day. Age-appropriate oral hygiene reinforcement was provided to all participants. Standardized photographs, ICDAS II scoring, and DIAGNOdent readings were repeated immediately post-treatment and at the 6-month follow-up. Inter-examiner reliability was deemed almost perfect for ICDAS II assessments (weighted kappa = 0.87; 95% confidence interval (CI) 0.81–0.93) and excellent for DIAGNOdent readings (intraclass correlation coefficient = 0.94; 95% CI 0.91–0.97).

2.8 Statistical analysis

All statistical analyses were performed using SPSS Statistics 27 (IBM, Armonk, NY, USA). Initial evaluations revealed that the raw distributions of ΔE, ICDAS II and DIAGNOdent departed significantly from normality (Shapiro-Wilk and Kolmogorov-Smirnov tests, $p < 0.001$). Consequently, between-group comparisons were conducted using the Kruskal-Wallis test with Bonferroni-corrected Dunn *post hoc* tests. Within-group time-course comparisons used the Friedman test with Bonferroni-corrected Wilcoxon signed-rank *post hoc* tests. Tables report the median (interquartile range (IQR)) as the primary descriptive statistic and the mean (SD) as a secondary descriptive statistic. All tabulated between- and within-group statistical tests are inherently rank-based. Pairwise between-group comparisons of the secondary outcomes (ICDAS II and DIAGNOdent) include rank-based effect sizes ($r = |Z|/\sqrt{N}$, where N is the combined number of teeth in the two treatment groups being compared in each pairwise test). Analysis followed a per-protocol (complete-case) approach, and missing observations were not imputed. Of the 210 allocated teeth, six did not receive the allocated intervention, and four were lost to follow-up, leaving 200 teeth (4.8% attrition) for analysis. Notably, these losses were distributed evenly across all three study groups. Given this low and relatively balanced attrition rate, data imputation was deemed unnecessary. However, the absence of a formal intention-to-treat analysis is acknowledged as a methodological limitation.

The pre-registered primary analysis of color change was based on an unadjusted between-group comparison using the Kruskal-Wallis test. However, because a marked baseline ΔE imbalance emerged after randomization, two prespecified baseline-adjusted analyses were employed for the primary inference to appropriately handle this discrepancy. First, to account for the within-patient clustering of the two assessed teeth per child (FDI 11 and 21), a linear mixed-effects model was fitted for each outcome using restricted maximum likelihood estimation. In this model, patient was designated as a random intercept and treatment group, time point, and baseline value as fixed effects (Outcome ~ Group + Time + Baseline + (1 | Patient)). This clustered, baseline-adjusted model served as the primary inferential framework for the between-group comparisons; the computed intraclass correlation coefficients and full model outputs are provided in the **Supplementary material**. Second, an analysis of covariance (ANCOVA) was performed at the tooth level on the per-protocol dataset (n = 200 teeth). For this model, the change score (baseline ΔE minus 6-month ΔE) was the dependent variable, with treatment group designated as a fixed factor and baseline ΔE as a covariate. Additionally, a rank-based (Quade) ANCOVA was performed as a non-parametric check, and the foundational tooth-level rank tests (Kruskal-Wallis and Friedman) were retained to provide descriptive support. ANCOVA assumptions were verified on the model residuals before inference: standardized residuals were normally distributed (Shapiro-Wilk $W = 0.987$, $p = 0.183$) with no values exceeding |2.5|, regression slopes were homogeneous (group × baseline, $F(2,194) = 0.953$, $p = 0.388$), and variances were equal (Levene $F(2,197) = 1.215$, $p = 0.300$). One caveat applies to the adjustment: the P11-4 group showed minimal baseline overlap with the other treatment arms, with its interquartile ΔE range (16.6–25.0) lying almost entirely above those of RI (8.9–15.4) and P11-4 + FV (9.7–14.0). Consequently, the adjusted color estimate for the P11-4 group relies partially on extrapolation beyond the region of common support, and these results should therefore be carefully interpreted with this statistical limitation in mind. Statistical significance was set at $p = 0.05$ (two-sided).

3. Results

3.1 Participant flow

Of the 250 children initially assessed for eligibility, 105 met all criteria and were randomized into three study arms (35 patients per group), contributing to a total of 210 teeth (Fig. 1). Following randomization, six teeth did not receive their allocated intervention (RI, n = 2; P11-4, n = 4), and four teeth were lost to follow-up (RI, n = 2; P11-4 + FV, n = 2). Consequently, the per-protocol analysis included 200 teeth (RI, n = 66; P11-4, n = 66; P11-4 + FV, n = 68). No adverse events, allergic reactions, or instances of post-treatment sensitivity were reported in any group during follow-up. Baseline demographic characteristics of the study participants are summarized in Table 1.

3.2 Color change (ΔE)

All intervention groups showed a significant within-group improvement in ΔE over time ($p < 0.001$ for all). At baseline, the P11-4 group exhibited a significantly higher ΔE (mean 20.84, SD 5.33) than RI (12.27, SD 4.17) and P11-4 + FV (11.81, SD 2.85; Kruskal-Wallis $H = 87.42$, $p < 0.001$, eta-squared = 0.44), whereas the baseline values did not differ significantly between the RI and P11-4 + FV groups. At the 6-month follow-up, P11-4 + FV achieved the lowest residual ΔE (4.45, SD 2.86), RI showed an intermediate but stable value (7.27, SD 7.18), and P11-4 had the highest residual ΔE (9.16, SD 3.74; Table 2).

The unadjusted net color change initially favored P11-4 (mean 13.10, SD 4.10) over RI (10.92, SD 8.42) and P11-4 + FV (10.09, SD 4.00; $H = 26.01$, $p < 0.001$). However, given the marked baseline imbalance, ANCOVA with baseline ΔE as a covariate was performed at the tooth level (n = 200). The covariate proved to be a strong predictor ($F(1,196) = 30.65$, $p < 0.001$); following this adjustment, the overall between-group effect on color change was not significant ($F(2,196) = 2.51$, $p = 0.086$, partial eta-squared = 0.04). The estimated marginal means at the grand-mean baseline (14.62) were RI = 12.34 (95% CI 10.50–14.18), P11-4 + FV = 11.91 (95% CI 10.04–13.79), and P11-4 = 8.92 (95% CI 6.75–11.09).

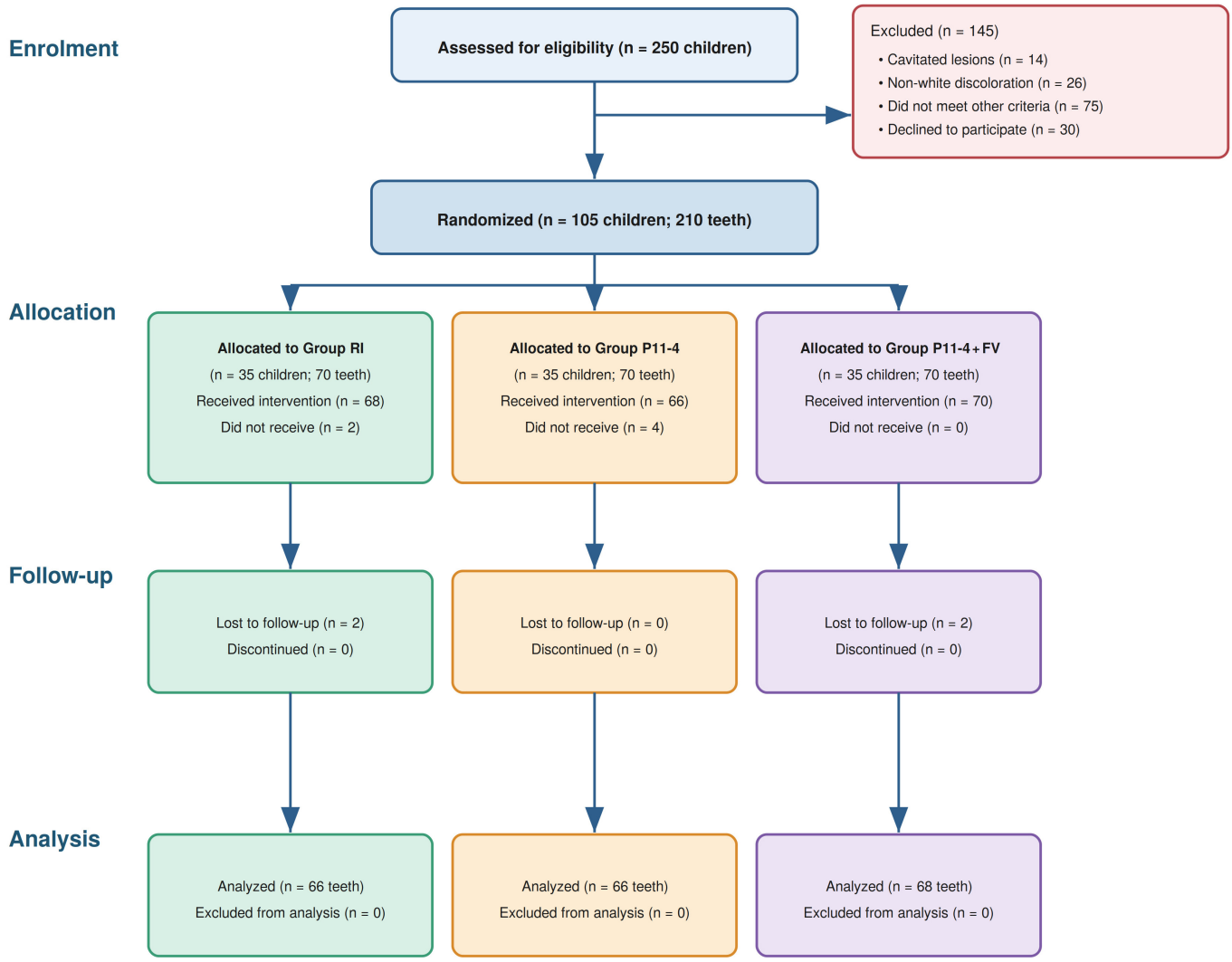

FIGURE 1. CONSORT 2010 flow diagram. A total of 105 children were enrolled and contributed 210 eligible non-cavitated white spot lesions. Randomization was performed at the patient level (35 patients per group); both maxillary central incisors (FDI 11 and 21) per child were assigned to the same group. Numbers are reported at the tooth level (the pre-specified unit of analysis): 210 teeth were allocated (RI, n = 70; P11-4, n = 70; P11-4 + FV, n = 70). Six teeth did not receive the allocated intervention (RI, n = 2; P11-4, n = 4); four teeth were lost to follow-up (RI, n = 2; P11-4 + FV, n = 2). Per-protocol analysis: 200 teeth (RI, n = 66; P11-4, n = 66; P11-4 + FV, n = 68). RI, resin infiltration; FV, fluoride varnish; FDI, Fédération Dentaire Internationale.

TABLE 1. Baseline demographic characteristics of participants, by treatment group.

Characteristic	Resin infiltration	P11-4	P11-4 + FV
Patients randomized, n	35	35	35
Age, years, mean (SD)	10.3 (1.9)	10.1 (1.8)	10.0 (1.9)
Sex, female/male, n (%)	18 (51.4)/17 (48.6)	13 (37.1)/22 (62.9)	15 (42.9)/20 (57.1)
Recruitment site, Al-Azhar/October 6 University, n (%)	21 (60.0)/14 (40.0)	19 (54.3)/16 (45.7)	15 (42.9)/20 (57.1)

Values are presented as n (%) or mean (standard deviation) unless otherwise noted. Age, sex, and recruitment-site data are based on the original enrollment records for all 105 participants. The number of participants randomized are consistent with the CONSORT flow diagram (Fig. 1) already reported in the manuscript. FV, fluoride varnish; SD, standard deviation.

TABLE 2. Color change (ΔE) at baseline, immediately post-treatment, and 6-month follow-up.

Time point	Resin infiltration	P11-4	P11-4 + FV
Baseline	11.29 (8.9–15.4)/12.27 (4.17)^{a,A}	20.04 (16.6–25.0)/20.84 (5.33)^{b,A}	12.57 (9.7–14.0)/11.81 (2.85)^{a,A}
Immediate post-treatment	7.42 (5.0–10.1)/7.83 (3.46)^{a,B}	13.15 (11.2–18.4)/14.81 (4.59)^{b,B}	7.28 (4.8–11.6)/8.68 (4.75)^{a,B}
6-month follow-up	6.04 (3.6–9.5)/7.27 (7.18)^{b,C}	9.27 (6.5–11.7)/9.16 (3.74)^{c,C}	3.93 (2.4–6.0)/4.45 (2.86)^{a,C}
Net change	8.99 (6.0–12.4)/10.92 (8.42)^{a}	13.34 (10.1–16.0)/13.10 (4.10)^{b}	8.25 (6.8–12.4)/10.09 (4.00)^{a}

Values are presented as median (interquartile range)/mean (standard deviation). Different lowercase superscript letters $^{(a,b,c)}$ within a row indicate significant between-group differences (unadjusted, $p < 0.05$); different uppercase superscript letters $^{(A,B,C)}$ within a column indicate significant within-group differences over time ($p < 0.05$). Between-group: Kruskal-Wallis test with Bonferroni-corrected Dunn post hoc tests; within-group: Friedman test with Bonferroni-corrected Wilcoxon post hoc tests. ANCOVA adjusting for baseline ΔE (tooth-level, n = 200): overall group effect F(2,196) = 2.51, p = 0.086 (partial eta-squared = 0.04). Estimated marginal means at grand-mean baseline (14.62): RI = 12.34; P11-4 + FV = 11.91; P11-4 = 8.92; no significant pairwise differences after Bonferroni correction (all $p > 0.05$). Rank-based ANCOVA (Quade test) sensitivity analysis: p = 0.094. ΔE, color difference; ANCOVA, analysis of covariance; FV, fluoride varnish; RI, resin infiltration.

Bonferroni-corrected pairwise comparisons showed no significant differences among the groups (all $p > 0.05$). Furthermore, a sensitivity ANCOVA evaluating the 6-month ΔE values ($p = 0.080$) and a non-parametric rank-based Quade ANCOVA ($p = 0.094$) were consistent. In the patient-clustered mixed-effects model, which served as the primary inferential framework for this study, the between-group effect on color change was likewise non-significant ($F(2,103) = 2.41$, $p = 0.094$). It must be noted that because the baseline ΔE distribution of the P11-4 group overlapped only partially with those of the other arms, its adjusted estimate relies partly on extrapolation beyond the region of common support; consequently, the overlapping confidence intervals should be interpreted with this statistical limitation in mind.

3.3 ICDAS II scores

All groups showed significant within-group improvements in ICDAS II scores over the observation period ($p < 0.001$ for all). At baseline, all assessed teeth had an ICDAS II score of 2.00 (SD 0.00), in strict accordance with the trial's eligibility criterion. Immediately post-treatment, RI produced the most rapid improvement (mean 1.32, SD 0.94), with scores significantly lower than P11-4 (2.00, SD 0.00; $Z = -3.61$, $p = 0.001$, $r = 0.31$) and P11-4 + FV (2.00, SD 0.00; $Z = -3.61$, $p = 0.001$, $r = 0.31$), reflecting the immediate optical masking effect of resin infiltration. At 6 months, RI retained the lowest score (0.67, SD 0.95), significantly lower than P11-4 (1.30, SD 0.96; $Z = -3.16$, $p = 0.005$, $r = 0.28$). RI and P11-4 + FV (0.97, SD 1.01) did not differ ($Z = -1.65$, $p = 0.290$, $r = 0.14$), nor did P11-4 and P11-4 + FV differ ($Z = 1.50$, $p = 0.400$, $r = 0.13$). These findings indicate similar long-term visual lesion outcomes between the RI and P11-4 + FV interventions regarding sustained visual lesion control (Table 3).

3.4 DIAGNOdent readings

All groups demonstrated significant within-group changes in DIAGNOdent readings over time (RI and P11-4 + FV, $p < 0.001$; P11-4, $p = 0.001$), although the magnitudes of these changes varied markedly. Specifically, RI (Kendall's $W = 0.51$, large effect) and P11-4 + FV ($W = 0.63$, large effect) showed sustained reductions, while P11-4 showed only a small intragroup effect ($W = 0.11$). At baseline, RI had the highest DIAGNOdent reading (mean 4.93, SD 3.41), exceeding P11-4 (2.12, SD 1.04) and P11-4 + FV (2.51, SD 2.16; $H = 44.58$, $p < 0.001$). By the 6-month follow-up, P11-4 + FV achieved the lowest reading (1.10, SD 0.94), significantly below P11-4 monotherapy (3.79, SD 3.26; $Z = 6.87$, $p < 0.001$, $r = 0.59$) within the two non-resin arms. The comparison with RI (1.92, SD 1.34; $Z = 3.58$, $p = 0.001$, $r = 0.31$) is reported for completeness but is confounded by the resin optical pathway (as detailed in the Methods section) and thus does not represent a direct biological comparison. The P11-4 group showed a significant increase in DIAGNOdent reading between immediate post-treatment (1.77, SD 0.48) and 6 months (3.79, SD 3.26; Wilcoxon $p < 0.001$; hereafter "fluorescence rebound"), with values exceeding baseline in several cases (Table 4, Figs. 2,3).

3.5 Primary clustered (mixed effects) analysis

The intraclass correlation coefficient computed at the patient level ranged from 0.18 to 0.27 across outcomes. This finding confirmed a modest yet non-negligible clustering effect for the two teeth treated within each child, thereby robustly supporting the selection of the patient-clustered model as the primary inferential framework for this study. In this model, the overall between-group effect remained non-significant for color change ($F(2,103) = 2.41$, $p = 0.094$) and significant for the 6-month ICDAS II ($F(2,103) = 6.18$, $p = 0.003$) and DIAGNOdent ($F(2,103) = 22.84$, $p < 0.001$) outcomes. These inferences were qualitatively consistent with the tooth-level analyses, which are retained as descriptive support (**Supplementary material**).

4. Discussion

This three-arm randomized controlled trial directly compared resin infiltration (RI), P11-4 monotherapy, and P11-4 combined with 5% sodium fluoride varnish (P11-4 + FV) in children with non-cavitated white spot lesions (WSLs). By utiliz-

TABLE 3. ICDAS II scores at baseline, immediately post-treatment and 6-month follow-up.

Time point	Resin infiltration	P11-4	P11-4 + FV
Baseline	2.00 (2.0–2.0)/2.00 (0.00)^{a,A}	2.00 (2.0–2.0)/2.00 (0.00)^{a,A}	2.00 (2.0–2.0)/2.00 (0.00)^{a,A}
Immediate post-treatment	2.00 (1.0–2.0)/1.32 (0.94)^{b,B}	2.00 (2.0–2.0)/2.00 (0.00)^{a,A}	2.00 (2.0–2.0)/2.00 (0.00)^{a,A}
6-month follow-up	0.00 (0.0–1.0)/0.67 (0.95)^{b,C}	2.00 (0.0–2.0)/1.30 (0.96)^{a,B}	0.00 (0.0–2.0)/0.97 (1.01)^{a,b,B}

Values are median (interquartile range)/mean (standard deviation). Different lowercase superscript letters $^{(a,b)}$ within a row indicate significant between-group differences (unadjusted, $p < 0.05$); different uppercase superscript letters $^{(A,B,C)}$ within a column indicate significant within-group differences over time ($p < 0.05$). ICDAS, International Caries Detection and Assessment System; FV, fluoride varnish; RI, resin infiltration.

TABLE 4. DIAGNOdent readings at baseline, immediately post-treatment and 6-month follow-up.

Time point	Resin infiltration	P11-4	P11-4 + FV
Baseline	3.83 (2.5–6.7)/4.93 (3.41)^{b,A}	1.67 (1.3–2.7)/2.12 (1.04)^{a,A}	2.00 (1.3–2.7)/2.51 (2.16)^{a,A}
Immediate post-treatment	1.67 (1.0–2.3)/1.71 (0.85)^{a,B}	1.67 (1.3–2.0)/1.77 (0.48)^{a,b,A}	2.00 (1.3–3.0)/2.29 (1.25)^{b,A}
6-month follow-up	1.94 (1.0–2.7)/1.92 (1.34)^{b,B}	2.67 (1.3–5.0)/3.79 (3.26)^{c,B}	0.89 (0.3–1.7)/1.10 (0.94)^{a,B}

Values are median (interquartile range)/mean (standard deviation). Different lowercase superscript letters $^{(a,b,c)}$ within a row indicate significant between-group differences (unadjusted, $p < 0.05$); different uppercase superscript letters $^{(A,B)}$ within a column indicate significant within-group differences over time ($p < 0.05$). Within-group test (Friedman): RI $p < 0.001$, Kendall $W = 0.51$ (large); P11-4 $p = 0.001$, $W = 0.11$ (small); P11-4 + FV $p < 0.001$, $W = 0.63$ (large). FV, fluoride varnish; RI, resin infiltration.

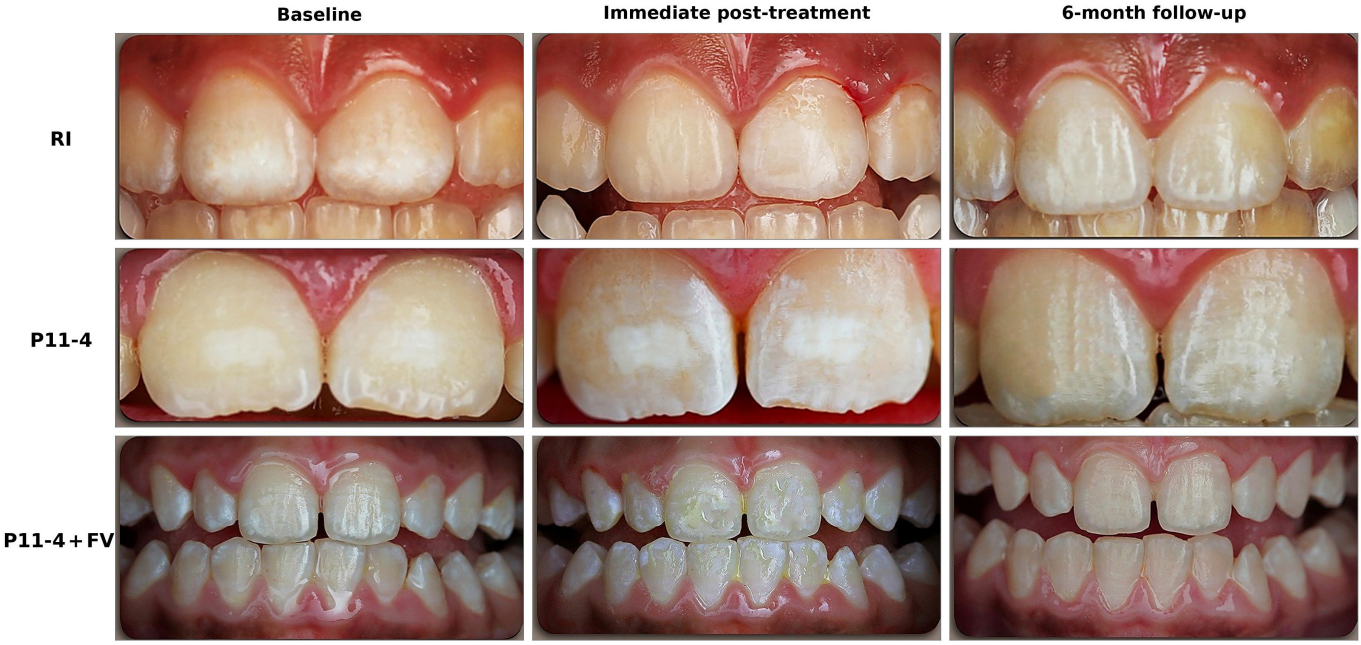

FIGURE 2. Representative clinical photographs of maxillary central incisors (FDI teeth 11 and 21) for the three treatment groups (rows) at baseline, immediately post-treatment and 6-month follow-up (columns). Top row: resin infiltration (RI). Middle row: self-assembling peptide P11-4. Bottom row: P11-4 with 5% sodium fluoride varnish (P11-4 + FV). Identifying facial features have been removed. FV, fluoride varnish.

ing parallel esthetic, visual, and fluorescence outcomes over 6 months, three principal findings emerged. First, after adjusting for the baseline ΔE imbalance, no statistically significant between-group difference in the final color outcome was detected; the apparent unadjusted superiority of P11-4 in net color change was explained by its higher baseline severity. Second, the protocols demonstrated distinct performance patterns on the secondary outcomes: RI produced the most rapid visual and immediate fluorescence improvements, P11-4 + FV yielded the most durable lesion-activity outcome at 6 months, and P11-4 monotherapy exhibited a clinically meaningful fluorescence rebound. Third, the differences among the protocols were outcome-specific, indicating that an intervention performing best on one measure did not necessarily excel on the others.

All three protocols improved lesion color to a similar degree. The estimated marginal means exhibited overlapping confidence intervals, and the effect of the treatment group

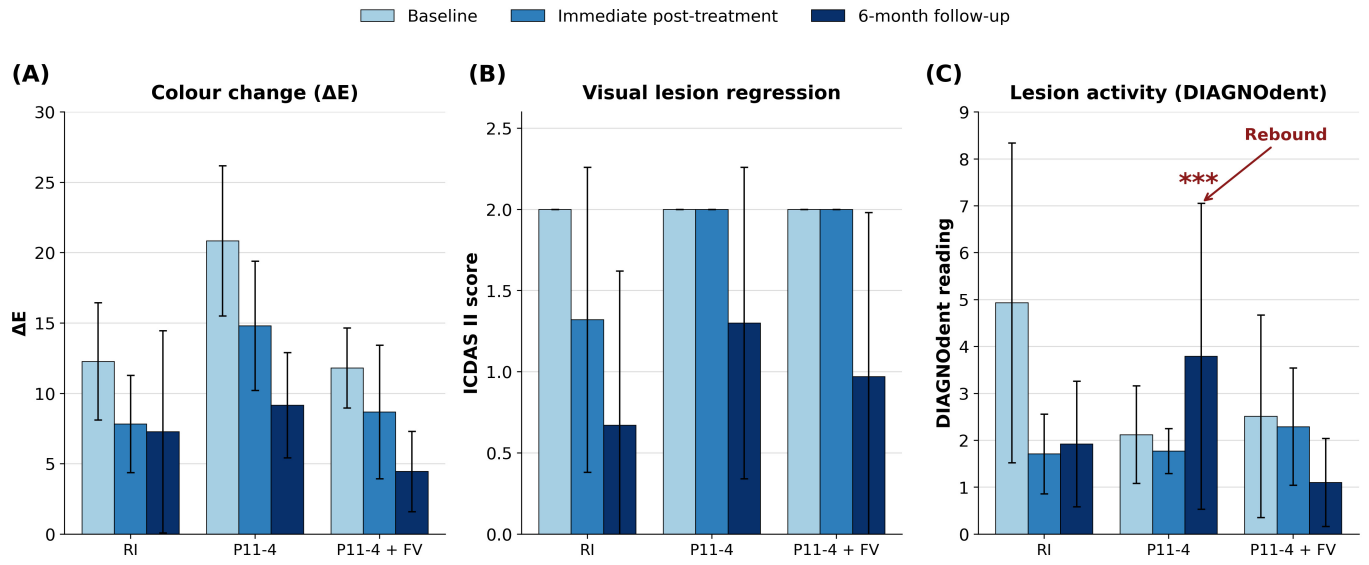

FIGURE 3. Outcome trajectories for the three treatment groups across the three assessment time points. (A) Color change (ΔE derived from CIELAB photographic analysis). (B) Visual lesion regression (ICDAS II score). (C) Lesion activity (DIAGNOdent readings). Time points are encoded by shading (light = baseline; medium = immediately post-treatment; dark = 6-month follow-up); groups are shown along the x-axis. Error bars represent one standard deviation. The triple asterisk (***) on the DIAGNOdent panel marks the significant rebound for P11-4 monotherapy between the immediate post-treatment assessment and the 6-month follow-up (Wilcoxon signed-rank test, $p < 0.001$). RI, resin infiltration; FV, fluoride varnish; ICDAS, International Caries Detection and Assessment System.

after adjusting for baseline severity was small (partial eta-squared = 0.04). Although the analysis of covariance (ANCOVA) was not statistically significant at the tooth level ($p = 0.086$), this finding indicates that a statistically significant difference was not detected; it does not demonstrate that the protocols are equivalent, as no formal equivalence margin was predefined. Even so, the result holds considerable clinical utility: because all three gave comparable color improvements, clinicians can select a protocol based on other treatment goals without sacrificing the final esthetic result. The clinically meaningful differences among the protocols appeared instead within the pre-specified secondary outcomes, ICDAS II and DIAGNOdent, which are reported here in strict accordance with CONSORT guidelines.

These findings extend previous *in vitro* evidence to a head-to-head pediatric clinical comparison. Wierichs *et al.* [6] reported that under demineralizing pH-cycling conditions, P11-4 alone could neither inhibit nor mask lesion progression, whereas RI provided effective masking, and the combination of P11-4 with fluoride showed an additive mineral-retention effect. The clinical pattern observed in the present trial is broadly consistent with these findings. P11-4 alone showed a partial visual response with a clear fluorescence rebound at 6 months, RI delivered immediate and stable optical masking, and P11-4 + FV achieved the most durable subsurface outcome despite receiving only a single fluoride application. Furthermore, in a 12-month trial involving children and adolescents, Atteya *et al.* [7] demonstrated that ICDAS and DIAGNOdent improvements following P11-4 application continued to develop between 6 and 12 months. This aligns with the durable DIAGNOdent reduction observed for P11-4 + FV at 6 months and suggests that longer follow-up would likely reveal further improvement. Similarly, Shaalan *et al.* [8] reported significantly greater remineralization with P11-4 + FV than with fluoride alone at 6 months, supporting our interpretation that the durable benefit of P11-4 + FV reflects a genuine synergy rather than the effect of fluoride alone. The fundamental capacity of fluoride-based and adjunctive remineralizing regimens to reduce DIAGNOdent values in children with early enamel lesions has likewise been demonstrated [12].

Broader literature further contextualizes these results. A systematic review and meta-analysis by Bourouni *et al.* [3] reported mean post-RI ΔE improvements ranging from 3.1 to 6.8 units for non-post-orthodontic WSLs. The reduction in the mean ΔE in the RI group of the present trial (decreasing from 12.27 at baseline to 7.27 at 6 months) is broadly consistent with this range, providing supporting evidence for the external validity of our findings. The clinical safety and quality of resin infiltration in pediatric settings have likewise been documented [13]. Additionally, a network meta-analysis by Xie *et al.* [5] ranked P11-4 with fluoride above both P11-4 monotherapy and resin infiltration for remineralization efficacy across the included trials. The present clinical data show a similar pattern for the DIAGNOdent secondary outcome, where P11-4 + FV achieved the lowest residual value at 6 months [5]. Similarly, a meta-analysis by Keeper *et al.* [4] reported a pooled standardized mean difference favoring P11-4-based regimens over control for lesion arrest. Our observation of a DIAGNOdent fluorescence rebound in the P11-4 monotherapy group, but notably not in P11-4 + FV, strongly corroborates their conclusion that fluoride co-administration is critical for sustained lesion arrest [4]. While direct comparisons are inherently limited by differences in WSL etiology (post-orthodontic in the studies of Knösel *et*

al. [14] and Gu *et al*. [15] versus developmental lesions in the present trial) and population age demographics, the visual stability of RI in our data remains broadly consistent with the 6- to 12-month ΔE values previously reported for those adolescent and adult cohorts. Furthermore, the somewhat higher residual ΔE observed in our study (mean 7.27) most likely reflects the deeper and broader developmental lesions enrolled, rather than any inferior protocol performance.

The residual ΔE of the RI group at the 6-month follow-up (mean 7.27, SD 7.18; median 6.04) warrants careful interpretation. Paravina *et al*. [16] reported a CIELAB 50:50% perceptibility threshold of ΔE*ab = 1.2 and a 50:50% acceptability threshold of ΔE*ab = 2.7; notably, our RI mean exceeded both benchmarks. However, because these thresholds were established using adult observer panels, their direct applicability to esthetic judgements in children aged 7–14 years and their caregivers remains uncertain. Children's color perception and parental esthetic expectations may differ significantly from those of adults, highlighting a potential need for future pediatric-specific calibration. Three additional points further qualify the interpretation of this outcome. First, the RI outcome was stable, with negligible drift between immediate post-treatment (7.83, SD 3.46) and the 6-month assessment (7.27, SD 7.18). Second, the wide SD indicates substantial heterogeneity: a subset of RI-treated teeth reached residual ΔE values below 2.7, while others did not. Third, these data suggest that while RI produces a stable population-level mean improvement, the final esthetic outcome is not uniformly optimal for all lesions. Consequently, for severely demineralized lesions, RI may need to be combined with adjunctive measures such as bleaching, repolishing, or partial enamel reshaping. P11-4 + FV achieved the lowest residual ΔE (4.45, SD 2.86), bringing the population mean closer to, but still slightly above, the adult-derived acceptability threshold.

The significant DIAGNOdent fluorescence rebound in the P11-4 monotherapy group represents a central clinical finding of this trial. Three distinct mechanisms may contribute to this phenomenon: (i) renewed demineralization due to incomplete lesion arrest; (ii) residual subsurface bacterial-porphyrin fluorescence that becomes detectable only as the immediate post-treatment surface light scattering subsides; and (iii) an incomplete initial seal at the lesion-interface, which permits the ongoing acid and metabolite diffusion. The parallel lag in ICDAS II scores is consistent with mechanisms (i) and (iii) being dominant, although the current trial design precludes a definitive clinical distinction between these underlying pathways.

The interpretation of the P11-4 monotherapy rebound is naturally constrained by the absence of a dedicated fluoride-varnish-only comparator arm. However, indirect evidence robustly supports a treatment-specific interpretation. Contemporary pediatric data indicate that standard fluoride-based remineralizing regimens produce modest yet sustained reductions in DIAGNOdent readings over 6 months [12]. In stark contrast, the P11-4 monotherapy rebound observed in this study (mean 3.79, SD 3.26) substantially exceeds those expected residual values. This significant discrepancy supports the inference that the observed rebound reflects a specific shortcoming of the P11-4 monotherapy rather than a generic disease trajectory. Furthermore, previous studies have consistently shown that P11-4 combined with fluoride outperforms fluoride alone regarding subsurface remineralization. This historical consensus reinforces our interpretation that the highly durable P11-4 + FV outcome reflects genuine synergy [7, 8]. Future trials should include a fluoride-varnish-only arm alongside the active protocols to enable direct comparison.

A secondary methodological consideration involves DIAGNOdent measurements acquired over a resin-infiltrated surface. Because the physical resin layer alters the optical pathway of the laser-induced fluorescence, the dramatic post-treatment reduction observed in the RI group reflected not only real lesion improvement but also an artificial reduction caused by the resin physically blocking the diagnostic laser. Consequently, DIAGNOdent value in the RI group should not be interpreted as direct measure of remineralization comparable to that seen in the P11-4 + FV group; rather, they represent lesion-activity reading obtained under altered optical conditions. Conversely, P11-4 + FV achieved the lowest overall 6-month DIAGNOdent reading (1.10, SD 0.94), significantly below both RI and P11-4 despite a single fluoride application, supporting a synergistic mechanism consistent with the additive *in vitro* effect reported by Wierichs *et al*. [6] and previous clinical observations [7, 8].

Clinically, these results provide comprehensive, evidence-based guidance for treatment selection in pediatric WSL management, driven primarily by the overarching therapeutic goal. Where rapid single-visit esthetic correction is the primary goal, RI remains an effective option, provided clinicians acknowledge the caveat that adjunctive measures may be required for severely chromatic lesions. Conversely, for children assessed as high caries risk using validated activity-based criteria, where sustained subsurface remineralization is the primary goal, P11-4 + FV is recommended. For low- and moderate-risk children presenting with developmental WSLs of stable, inactive appearance, either RI or P11-4 + FV represents a clinically appropriate first-line choice. In these instances, final treatment selection should be carefully individualized, guided by the child's age, baseline cooperation level, and the specific esthetic expectations of the family.

Particularly for younger or less cooperative patients, P11-4 + FV offers a significantly shorter chair-time and a simplified single-application protocol, both of which can drastically improve patient tolerability and compliance. In contrast, RI requires prolonged rubber dam isolation, though it remains the optimal choice when immediate and predictable optical masking is clinically required. Therefore, shared decision-making with the child and guardian should address the trade-off between the immediate esthetic benefit of RI and the biologically durable remineralization offered by P11-4 + FV. P11-4 monotherapy showed a significant fluorescence rebound by the 6-month mark; its standalone use necessitates caution. If this monotherapy is utilized, fluoride co-administration or repeat P11-4 dosing should be considered at each routine recall visit (typically every 3–6 months in a pediatric preventive program). Retreatment should be triggered if the DIAGNOdent reading returns above the lesion-active threshold or if the ICDAS II score increases. In this context, routine fluoride varnish application at each recall represents a simple,

evidence-based adjunct that aligns seamlessly with standard pediatric preventive care pathways.

This trial has several methodological limitations. First, despite the utilization of a concealed computer-generated sequence, randomization resulted in the P11-4 group beginning the trial with a markedly higher baseline ΔE (eta-squared = 0.44). This was likely a chance statistical imbalance that was subsequently amplified by patient-level allocation of two highly correlated central incisors per child. Because the initial statistical power calculation was framed at the tooth level and did not account for this within-patient clustering effect, the baseline-adjusted color comparison was probably underpowered. Consequently, the non-significant result for color change reflects a failure to detect a statistical difference rather than an absolute proof of clinical equivalence; future clinical trials should therefore employ randomization stratified by baseline lesion severity. Second, the 6-month follow-up limits durability conclusions, and a minimum of 12 months is recommended to confirm whether the fluorescence advantage of P11-4 + FV, the color stability of RI, and the ICDAS II gains persist [7]. Third, fluoride varnish was applied only once. While this methodological choice strengthens the internal attribution, since the durable P11-4 + FV effect cannot be ascribed to repeated dosing, it differs from routine repeated-varnish practice, so the durability seen here should not be assumed to generalize. Fourth, operator masking was inherently not feasible because the clinical application procedures are visually distinct, and operator-level variability was not modeled, although inter-examiner reliability for outcome assessment was high. Fifth, the analysis was per-protocol with no imputation; attrition was low (4.8%) and balanced across groups, but no formal intention-to-treat analysis was performed, and the potential for attrition bias cannot be completely excluded. Finally, critical behavioral variables such as home oral hygiene and dietary habits were not quantified at follow-up and may have contributed to the P11-4 monotherapy rebound; ICDAS II, DIAGNOdent, and ΔE each capture fundamentally different lesion facets, and none of these outcomes provide a direct biological measure of remineralization.

5. Conclusions

After adjusting for baseline lesion severity, no statistically significant between-group difference in esthetic color outcome was detected at the 6-month follow-up in children treated for non-cavitated white spot lesions. Regarding the secondary clinical outcomes, resin infiltration produced the most rapid visual and immediate fluorescence improvement, a phenomenon directly attributable to the optical masking by the infiltrant resin. Within the two biologically focused non-resin study arms, the application of P11-4 combined with fluoride varnish produced the most durable reduction in lesion-activity fluorescence at 6 months, despite utilizing only a single fluoride application. Conversely, P11-4 monotherapy resulted in a significant fluorescence rebound over the same period. This distinct outcome pattern is highly consistent with a biochemical synergy between the peptide scaffold and fluoride; however, in the absence of a dedicated fluoride-only comparator group, this synergy cannot be definitively established. Ultimately, the selection of an appropriate minimally invasive treatment protocol should be guided by the primary clinical goal, whether prioritizing immediate esthetic correction or durable subsurface remineralization, and these distinct therapeutic profiles must be confirmed in longer-term trials that explicitly include a fluoride-only control arm.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

AME and DYE—conceptualized and designed the research study. AS, DYE and NAS—performed the clinical interventions and acquired the data. DYE and AS—executed the standardized photographic acquisition, conducted the CIELAB analysis, and curated the resulting dataset. NAS—managed and coordinated the trial operations and resources at the second study site. SB—provided the study materials and methodological expertise in minimally invasive caries management. SAA—analyzed the data. AME, DYE and SAA—drafted the initial manuscript. AME, SAA, AS and NAS—critically revised the manuscript for important intellectual content. All authors contributed to the final editorial changes. Furthermore, all authors have read and approved the final version of this manuscript, confirming they have participated sufficiently in the work to take public responsibility for all aspects of the research.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was granted by the institutional research ethics committees of the Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt (initial approval code: P-PD-24-02, issued prior to enrollment; final approval code: REC-PD-25-01, issued after study completion for documentation and publication) and the Faculty of Dentistry, October 6 University, Giza, Egypt (approval code: RECO6U/6-2024). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent for participation and publication was obtained from the parents or legal guardians of all participating children. Written assent was also obtained from the children who were capable of providing assent, in accordance with age and ethical requirements. The trial was prospectively registered (ClinicalTrials.gov NCT06708481).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/2095417438638096384/attachment/Supplementary%20material.docx.

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