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ORIGINAL ARTICLE

Thirty-six-month follow-up of cervical composite restorations placed with an MDP-free universal adhesive system using different adhesive protocols: a randomized clinical trial

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Abstract

Objectives To evaluate the influence of different application strategies on the clinical behavior of an MDP-free universal adhesive placed in non-carious cervical lesions (NCCLs) over the course of 36 months.

Materials and methods Thirty-one patients participated in this study ($N=31$). One hundred twenty-four restorations were assigned to four groups: We used the self-etch strategy on groups with (SE-et) and without (SET) selective enamel etching, and the etch-and-rinse strategy on groups with dry (ER-D) and moist (ER-M) dentin. After applying the MDP-free universal adhesive (Xeno Select universal adhesive, Dentsply Sirona), cavities were filled using EvoluX composite resin (Dentsply Sirona). The restorations were evaluated at baseline and after 36 months according to World Dental Federation (FDI) and US Public Health Service (USPHS) criteria. Friedman's repeated-measures analysis of variance rank ($\alpha=0.05$) was used for statistical analysis.

Results We evaluated the 31 patients after 36 months. Forty-two restorations were lost (ER-D = 5, ER-M = 7, SE-et = 14, SET = 16). The 36-month retention/fracture rates (95% confidence interval) were 83.9% for ER-D, 77.4% for ER-M, 54.9% for SE-et, and 48.4% for SET. ER strategy showed better retention rate than SE strategy ($p<0.05$). Thirty-four restorations (ER-D = 6, ER-M = 10, SE-et = 10, SET = 8) showed marginal staining per FDI criteria and 15 restorations (ER-D = 1, ER-M = 2, SE-et = 6, SET = 6) showed marginal staining per USPHS criteria. No restorations showed postoperative sensitivity or recurrence of caries.

Conclusion The retention rate of Xeno Select universal adhesive was poor, mainly in the self-etch strategy.

Trial registration REBEC clinical registry under protocol RBR-4wh4sh.

Clinical relevance MDP-free universal adhesive behavior depends on the bonding strategy used.

Keywords Non-carious cervical lesions · Universal adhesive · Randomized clinical trial · Retentio rate · Self-etch strategy · Etch-and-rinse adhesive

Introduction

The worldwide prevalence of non-carious cervical lesions (NCCLs) among adults is 46.7%, and the issue is more prevalent in older populations than younger ones. Americans have the highest prevalence of NCCLs among different geographical regions, and general populations are more inclined to present these lesions than specific ones [1]. The clinical manifestations of NCCLs can affect a patient's quality of life, and treatment helps prevent problems such as dentin hypersensitivity and gingival recession, among others [2].

Restorative treatment is used to treat NCCLs. The use of universal adhesives has drawn attention mainly because

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of their versatility; theoretically, they are adhesive systems that can be used as self-etch (SE) adhesives, with or without selective enamel etching, or as etch-and-rinse (ER) adhesives [3, 4]. In addition, these new adhesive systems are typically presented as one-bottle materials, following a trend among dental adhesive manufacturers to provide products with simpler use techniques in an effort to reduce the risk of error during use [5–7].

Usually, universal adhesives are similar to simplified SE adhesives, but contain specific functional monomers to provide better bonding to the enamel and dentin substrates. The best known of these monomers is 10-methacryloyloxydecyl dihydrogen phosphate (MDP) [8, 9]. However, several universal adhesives available in the market do not contain 10-MDP, but other functional monomers such as PENTA (dipentaerythritol pentaacrylate monophosphate) or GPDM (glycero-phosphate dimethacrylate) [4, 10, 11].

Several in vitro studies evaluating bond durability to dentin showed stable chemical bonding produced by universal adhesive containing 10-MDP in comparison to MDP-free adhesives [12]. Nevertheless, there is no consensus on whether the presence of MDP is critical to improve the performance of universal adhesives [11, 13, 14].

Although in vitro studies are very important for initial screening of adhesive performance, laboratory tests cannot faithfully predict an adhesive system's clinical behavior [15, 16]. Therefore, clinical evaluations of universal adhesive systems have been carried out to assess their reliability. A closer view regarding clinical studies showed that the majority of clinical results available in the literature are short-term follow-ups (6 to 24 months) evaluating MDP-containing universal adhesives [17–25]. Only a few clinical studies have been published with 36–60 months of clinical evaluation, usually evaluating the first MDP-containing universal adhesive available on the market [26–28].

It is worth mentioning that it is still unclear whether differences exist, mainly in the retention rate when ER and SE modes are compared [25, 27, 29]. This seems to be confirmed by a recent overview of universal adhesives published by Nagaskar et al. [11]. The authors concluded that longer follow-ups regarding the clinical performance of universal adhesives are lacking, mainly results supporting the claim that these new adhesive materials can be used with any adhesive strategy (SE or ER).

Therefore, the purpose of this double-blind, randomized clinical trial was to evaluate the influence of different application strategies on the clinical behavior of an MDP-free universal adhesive (Xeno Select universal adhesive, Dentsply Sirona, Konstanz, Germany) placed in NCCLs over the course of 36 months using World Dental Federation (FDI) and US Public Health Service (USPHS) evaluation criteria. The main null hypothesis we tested was that bonding to NCCLs using the SE strategy—regardless of association with selective enamel etching or ER—would result in similar retention levels (primary outcome) over 36 months of clinical service when applied to dry or moist dentin. Also, as secondary outcomes (marginal staining, marginal adaptation, postoperative sensitivity, and recurrence of caries) were evaluated, the null hypothesis we tested was that bonding to NCCLs using the SE strategy—regardless of association with selective enamel etching or ER—would result in similar marginal staining, marginal adaptation, postoperative sensitivity, and recurrence of caries over 36 months of clinical service when applied to dry or moist dentin.

Methods and materials

Study design

The experimental design followed the Consolidated Standards of Reporting Trials (CONSORT) statement [30]. This was a randomized, double-blind clinical trial, registered in the REBEC clinical registry under protocol RBR-4wh4sh. We carried out the study in the clinics of the Fluminense Federal University School of Dentistry from June 2014 to November 2014. All participants were informed about the nature and objectives of the study, but they were not aware of which teeth had received the specific treatments under evaluation.

Participant recruitment

The local ethics committee on investigations involving human subjects reviewed and approved the protocol and issued a consent form for this study (protocol 800.273/14). Written informed consent was obtained from all participants prior to starting the treatment.

Sample size calculation

The sample size calculation was based on the retention rates of Xeno III, IV, and V, and predecessors of the Xeno Select adhesive system from the same manufacturer (also known as Prime & Bond One Select in some countries; Dentsply Sirona, Konstanz, Germany). The retention rate was reported to be 96% at 18- to 24-month follow-up [31–34]. Using an α of 0.05, a power of 80%, and a two-sided test, the minimum sample size was 31 restorations in each group in order to detect a difference of 25% among the tested groups [35].

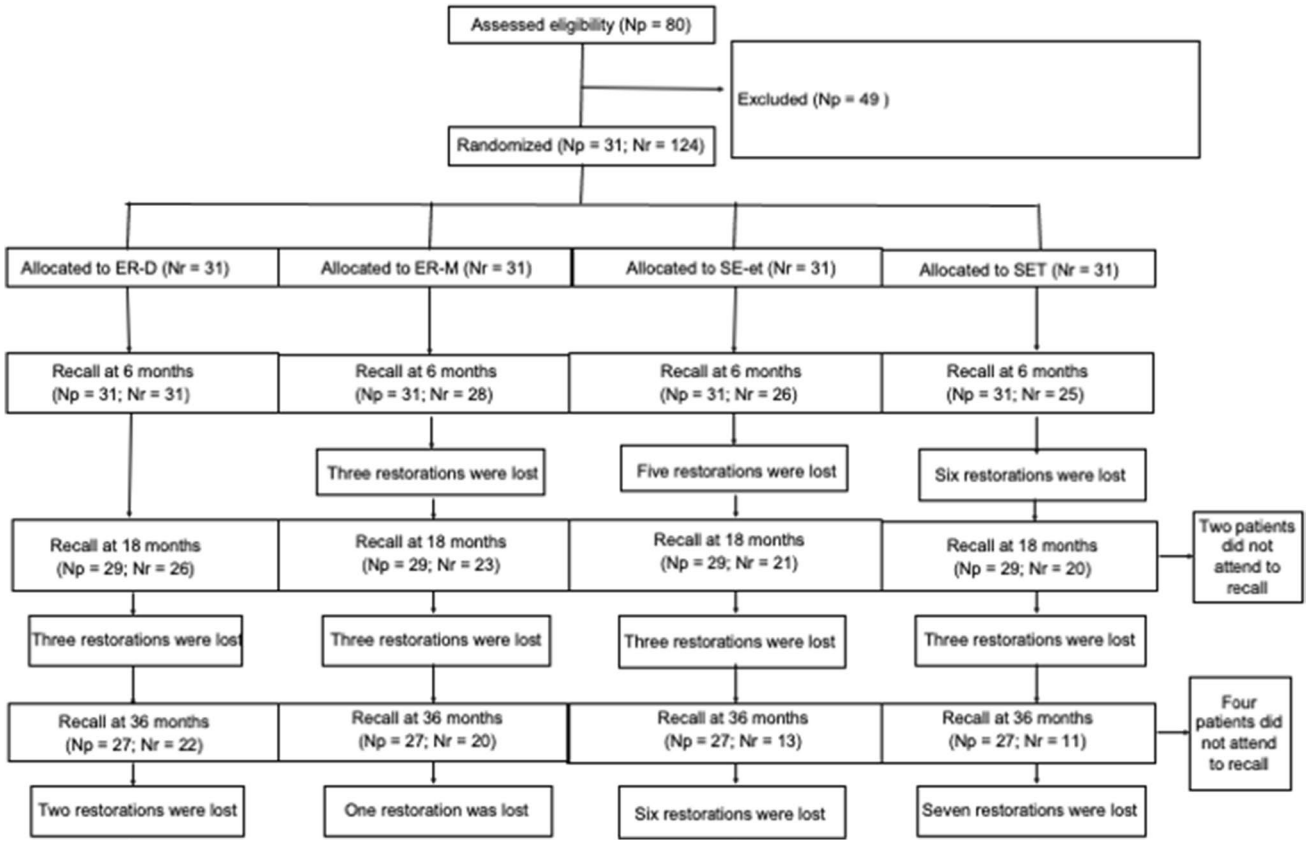

Fig. 1 Flow diagram of the study phases. Np, number of patients; Nr, number of restorations

Eligibility criteria

A total of 80 initial participants were examined by two calibrated dental students to determine whether they met the inclusion criteria (Fig. 1). Those who qualified for the study were recruited in the order in which they reported for the screening session, forming a convenience sample.

Evaluations were performed using a mouth mirror, an explorer, and a periodontal probe. Participants had to be in good general health, at least 18 years of age, have an acceptable oral hygiene level, and present with at least 20 teeth under occlusion. Participants were required to have at least four NCCLs to be restored in four different teeth. These lesions had to be non-carious, non-retentive, and deeper than 1 mm and had to involve both the enamel and dentin of vital teeth without mobility. The cavo-surface margin could not involve more than 50% of enamel [36].

All patients were given oral hygiene instructions before operative treatment. Patients with extremely poor oral hygiene, severe or chronic periodontitis, or heavy bruxism habits were excluded from the study.

Randomization and allocation concealment

The randomization was done on an intra-individual basis so that each subject ended up with four restorations, each one resulting from one of all possible combinations of adhesive strategy. These randomization schemes were performed using software available at http://www.sealedenvelope.com. A staff member not involved in the research protocol performed the randomization process with computer-generated tables. Details of the allocated groups were recorded on cards contained in sequentially numbered, opaque, sealed envelopes. Opening the envelope on the day of the restorative procedure revealed each participant's allocation assignment. The operator was not blinded to group assignment when administering interventions; however, participants and evaluators were blinded to the group assignments.

Interventions: Restorative procedure

All patients selected for this study received dental prophylaxis with a suspension of pumice and water in a rubber cup and signed an informed consent form 2 weeks before the restorative procedures were initiated.

Table 1 Dentin sclerosis scale

Category	Criteria
1	No sclerosis present; dentin is light yellowish or whitish, with little discoloration; dentin is opaque, with little translucency or transparency
2	More sclerosis than in category 1 but less than halfway between categories 1 and 4
3	Less sclerosis than in category 4 but more than halfway between categories 1 and 4
4	Significant sclerosis present; dentin is dark yellow or even discolored (brownish); glassy appearance, with significant translucency or transparency evident

Adapted from Swift et al. [37]

The degree of sclerotic dentin from the NCCLs was measured according to the criteria described by Swift et al. [37] (Table 1). In order to calibrate this evaluation, the two operators were trained by the study director by observing 10 photographs that were representative of each score. Then, they evaluated 15 patients each on two consecutive days for calibration. These subjects had cervical restorations, but were not part of this project. Intraexaminer and interexaminer agreements of at least 85% were necessary before beginning the experimental evaluation [38]. The cavity dimensions in millimeters (height, width, and depth), the geometry of each cavity (evaluated by profile photograph and labeled as < 45°, 45–90°, 90–135°, and > 135°), the presence of an antagonist, and the presence of attrition facets were observed and recorded. Preoperative sensitivity was also evaluated by applying air for 10 s from a dental syringe placed 2 cm from the tooth surface and with an explorer. These features were recorded to allow comparison of the baseline features of the dentin cavities among experimental groups.

To calibrate the restoration procedure, the study director performed one restoration in each group to identify all steps involved in the application techniques. Then, the two operators, who were resident dentists with more than 5 years of clinical experience in operative dentistry, performed four restorations, one in each group, under the supervision of the study director in a clinical setting. Any restoration failures were shown to the operators prior to beginning the study. At this point, the operators were considered calibrated to perform the restorative procedures.

The calibrated operators restored all teeth under the supervision of the study director. All participants received four restorations—one of each experimental group type—in different lesions previously selected according to the inclusion criteria.

Before restorative procedures, the operators anesthetized the teeth with a 3% mepivacaine solution (Mepisv, Nova DFL, Rio de Janeiro, RJ, Brazil) and cleaned all lesions with pumice and water in a rubber cup, followed by rinsing and drying. Next, shades were selected using a shade guide. No additional retention or bevel was prepared.

A rubber dam was placed, and then the NCCLs received the Xeno Select adhesive system (Dentsply Sirona) applied in different modes: an ER approach keeping the dentin dry (ER-D) or moist (ER-M), and an SE approach either with selective enamel etching (SE-et) or without selective enamel etching (SET). These four modes defined the four different groups. The compositions, application modes, and batch numbers are described in Table 2. Some details of the restorative procedures included the following:

- ER/dry dentin group (ER-D)—We applied 37% phosphoric acid (Dentsply Sirona) to enamel (30 s) and dentin (15 s). Then, cavities were rinsed thoroughly for 30 s and slightly air-dried for 5 s to dry dentin without causing dentin dehydration. The adhesive system was applied sufficiently, wetting all cavity surfaces uniformly, and was gently agitated on the entire enamel and dentin surface for approximately 20 s, according to the manufacturer's recommendations (Table 2). Then, the adhesive was evaporated by gentle air thinning for 5 s and was light-cured (Radii Cal, SDI, Victoria, Australia) for 10 s (1200 mW/cm^2).
- ER/moist dentin group (ER-M)—All restorative procedures were similar to those described for the ER-D group. The only difference was that after acid rinsing, dentin was kept visibly moist.
- Selective enamel etch group (SE-et)—The 37% phosphoric acid (Dentsply Sirona) was applied for 15 s only on enamel. Then, it was rinsed thoroughly for 15 s and air-dried for 5 s, until the dentin was dried but not over dried. Following this, the adhesive was applied similarly to the way it was applied to the ER-D group.
- SE group (SET)—The adhesive system was applied as described in the ER-D group, without any prior acid etching. Then, the adhesive was evaporated by gentle air thinning for 5 s and was light-cured (Radii Cal, SDI) for 10 s (1200 mW/cm^2).

After adhesive application, EvoluX (Dentsply Sirona) resin composite was used in up to three increments, each one light-cured (Radii Cal, SDI) for 30 s. The restorations were finished immediately with fine and extra-fine #2200

Table 2 Materials (batch number), compositions, and application mode

Materials (batch number)	Compositions	Application mode (*)
Xeno Select (Dentsply Sirona) (1,401,001,212)	Bifunctional acrylate, acidic acrylate, functionalized phosphoric acid ester, water, tertiary butanol, initiator, stabilizer	Etch & rinse (ER-D and ER-M) 1. Apply etchant in enamel (30 s) and dentin (15 s), rinse for 30 s, air dry to remove excess of water; 2. Keep dentin dry (ER-D)** or moist (ER-M); 3. Apply the adhesive for 20 s with vigorous agitation, gently air thin for 5 s. Light cure for 10 s Selective enamel etching (SE-et) 4. Apply etchant for 15 s in enamel, rinse for 15 s, air dry to remove excess of water; 5. Keep dentin dry (do not overdry) 6. Apply the adhesive for 20 s with vigorous agitation, gently air thin for 5 s. Light cure for 10 s Self-etching (SET) 7. Do not use etchant; 8. Keep dentin dry (do not overdry) 9. Apply the adhesive for 20 s with vigorous agitation, gently air thin for 5 s. Light cure for 10 s
37% tooth conditioner gel (Dentsply Sirona) (941685F)	Phosphoric acid, surfactant, Aerosil 200, deionized water, and pigment	With the aid of the applicator tip, apply the acid conditioner to the dental structures in question, keeping it in contact with enamel for at least 15 s and with dentin for no more than 15 s. After conditioning, wash the surfaces with plenty of water, for at least the same amount of time as used for the conditioning, vacuuming with a saliva sucker
EvoluX (Dentsply Sirona) (Shade A3 – 681887E; Shade A3.5 – 697997E; Shade A1 – 673729E)	Silanized barium aluminum borosilicate glass, silanized barium fluoro aluminum borosilicate glass, dimethacrylate Bis-GMA and Bis-EMA, nanoparticulated silica, dyes, photoinitiators, inhibitors	Insert in the cavity increases of up to 2 mm and light cure each area of the surface of the restoration with a dental curing light appliance (wavelength of 470 nm, light power of 1200 mW/cm^2, for 30 s

*According to the manufacturer's instructions. *Abbreviations*: *Bis-GMA*, bisphenol-A-glycidyl dimethacrylate; Bis-EMA, bisphenol A dimethacrylate

**Manufacturer does not indicate application in dry dentin

diamond burs (KG Sorensen, Barueri, SP, Brazil). Polishing was performed with rubber points (Enhance, Dentsply) 1 week after placement of the restorations.

Clinical evaluation

Two experienced and calibrated dentists who were not involved with the restoration procedures (and therefore were blinded to the group assignment) performed the evaluation. For training purposes, the examiners observed 10 photographs that were representative of each score for each criterion. They evaluated 10 to 15 patients each on two consecutive days for calibration. These subjects had cervical restorations, but were not part of this project. Intraexaminer and interexaminer agreements of at least 85% were necessary before beginning the experimental evaluation [38]. After recording the parameters during evaluation using a standardized paper case report form, the evaluation papers were sent back to the research staff so that evaluators would still be blinded to group assignment during follow-up recalls.

The restorations were evaluated based on FDI [39] and classic USPHS criteria (adapted by Bittencourt et al. [40] and Perdigão et al. [41]) at baseline and after 6, 18, and 36 months of clinical service. Only the clinically relevant measures evaluating the adhesives' performance were used and scored according to previously described methods [18–20, 23, 26, 29]. The primary clinical outcome we measured was restoration retention/fracture, but the following secondary outcomes were also evaluated: marginal staining, marginal adaptation, postoperative sensitivity, and recurrence of caries. We evaluated spontaneous postoperative sensitivity 1 week after the restorative procedures.

These variables were ranked according to the criteria in the following scores: (1) FDI criteria (clinically very good, clinically good, clinically sufficient/satisfactory, clinically unsatisfactory, and clinically poor) and USPHS criteria (Alpha, Bravo, and Charlie). In the case of marginal staining and marginal adaptation, the Semiquantitative criteria (SQUACE) proposed by Hickel et al.[39] were used. Each evaluator outlined the extent of observed events in sketches of each restoration according to defined criteria (marginal staining and marginal adaptation); after that, each margin was assessed quantitatively as a proportion of total marginal length. Both examiners evaluated all of restorations only once and independently. When disagreements occurred during the evaluations, the examiners had to reach a consensus before dismissing a participant.

Statistical analysis

Statistical analysis followed the intention-to-treat protocol according to CONSORT (Consolidated Standards of Reporting Trials) guidelines [30]. Descriptive statistics were used to determine the distributions of the evaluated criteria.

The survival rates (retention/fracture data) of different groups of restorations were calculated using the Kaplan–Meier procedure, estimating the hazard ratios (HRs) and 95% confidence intervals. The log-rank test was used to compare the survival distributions of these restorations ($\alpha = 0.05$).

For the secondary outcomes (marginal staining, marginal adaptation, postoperative sensitivity, and recurrence of caries), we assessed the differences among the four groups' ratings after 36 months in each overall parameter (FDI and USPHS). Friedman's repeated-measures analysis of variance rank ($\alpha = 0.05$) was used. Cohen's kappa statistics were used to test interexaminer agreement ($\alpha = 0.05$; MedCalc Software, version 19.1, Mariakerke, Belgium).

Data from SQUACE were categorized into three scores: (1) marginal discrepancies involving less than 10% of the total length of the restoration, (2) those involving between 10 and 30%, and (3) those involving more than 30% [20, 23]. These groups were compared with Kruskal–Wallis and Mann–Whitney tests. In all statistical tests, we preset the level of significance to 5%.

Results

Forty-nine out of 80 patients were excluded from the study because they did not fulfill the inclusion criteria. Thus, a total of 31 subjects (15 male and 16 female), with a mean age of 45 years were enrolled in this study. One hundred twenty-four restorations were placed, with 31 in each group. All research subjects' baseline details and characteristics of the restored lesions are displayed in Table 3.

Performance of adhesive restorations

Good agreement was achieved between the examiners ($\kappa = 0.92$). All research subjects were evaluated at baseline and at 6-month recalls. Two patients did not attend the 18-month recall, and another two patients did not attend the 36-month recall. All of them had moved to other cities.

Retention/fracture

After 36 months of clinical evaluation, 42 restorations were lost (ER-D = 5, ER-M = 7, SE-et = 14, SET = 16). According to FDI and USPHS criteria, the 36-month retention/fracture rates (95% CIs) were as follows: ER-D = 83.9% (95% CI 66.4–93.0%), ER-M = 77.4% (95% CI 60.2–89.6%), SE-et = 54.9% (95% CI 37.8–70.9), and SE = 48.4% (95% CI 32.0–65.2%; Tables 4 and 5). Kaplan–Meier curves showed significant differences (log-rank test, $p = 0.0002$) among

Table 3 Characteristics of the research subjects and the non-carious cervical lesions (NCCL) per group

Characteristics of research subjects	Number of lesions			
Gender distribution				
Male	15			
Female	16			
Age distribution (years)				
20–29	0			
30–39	1			
39–49	6			
> 49	24			
Characteristics of NCCLs	**Number of lesions**			
	ER-D	ER-M	SE-et	SET
Shape (degree of angle)				
< 45	1	1	1	0
45–90	6	6	10	7
90–135	16	18	11	17
> 135	8	6	9	7
Cervico-incisal height (mm)				
< 1.5	4	5	4	3
1.5–2.5	12	10	12	12
2.5–4.0	11	13	10	12
> 4.0	4	3	5	4
Degree of sclerotic dentin				
1	15	16	15	15
2	7	8	5	10
3	6	6	8	4
4	3	1	3	2
Presence of antagonist				
Yes	29	28	30	29
No	2	3	1	2
Attrition facet				
Yes	16	15	20	19
No	15	16	11	12
Preoperative sensitivity (spontaneous)				
Yes	0	1	0	1
No	31	30	31	30
Preoperative sensitivity (air dry)				
Yes	7	9	12	9
No	24	22	19	22
Preoperative sensitivity (touch)				
Yes	7	11	14	9
No	24	20	17	22
Tooth distribution				
Anterior				
Incisor	7	5	3	4
Canines	4	4	4	3
Posterior				
Premolar	19	22	21	19
Molar	1	0	3	5
Arc distribution				
Maxillary	17	15	15	10
Mandibular	14	16	16	21

Abbreviations: *ER-D*, etch-and-rinse, dry dentin; *ER-M*, etch-and-rinse, moist dentin; *SE-et*, self-etch with selective enamel etching; *SET*, self-etch without selective enamel etching

the cumulative probability of the primary endpoint, which was loss of retention/fracture (Fig. 2). The paired comparisons among the four groups are given by the hazard ratios depicted in Table 6. We observed significant differences in (1) SET vs. ER-M (HR = 3.2; 95% CI 1.8–5.9) and SET vs. ER-D (HR = 3.44; 95% CI 1.88–6.2), meaning that cavities receiving SET were on average 2.2 and 2.4 times more likely to debond than those receiving the ER-M or ER-D bonding approaches at any given time, respectively; and (2) SE-et vs. ER-D (HR = 1.93; 95% CI 1.06–3.53), meaning that restorations bonded with SET are on average 0.93 times more likely to debond than those placed using ER-D.

Marginal staining

After 36 months of clinical evaluation, 31 restorations (ER-D = 6, ER-M = 10, SE-et = 7, SET = 8) showed marginal staining based on FDI criteria (Table 4). Fifteen restorations (ER-D = 1, ER-M = 2, SE-et = 6, SET = 6) showed marginal staining based on USPHS criteria (Table 5). No significant difference was found among groups after 36 months' recall time for either criterion ($p < 0.21$). When SQUACE was used, we observed no statistically significant difference among groups upon 36-month clinical evaluation ($p > 0.21$; Table 7).

Table 4 Number of evaluated restorations for each group classified according to the World Dental Federation criteria[39] in different follow-up times (6, 18, and 36 months)

FDI criteria		Baseline				6 months				18 months				36 months			
		ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET
Retention/fracture	**A**	31	31	31	31	30	28	25	25	26	23	17	20	22	20	11	11
	B	–	–	–	–	–	–	–	–	–	–	1	–	–	–	1	–
	C	–	–	–	–	–	–	1	–	–	–	1	–	–	–	1	–
	D	–	–	–	–	1	–	–	–	–	–	2	–	–	–	–	–
	E	–	–	–	–	–	3	5	6	3	6	8	9	5	7	14	16
Marginal adaptation	**A**	31	31	31	31	17	18	15	12	9	9	5	8	6	2	1	0
	B	–	–	–	–	13	10	11	13	17	14	14	11	15	14	12	10
	C	–	–	–	–	–	–	–	–	–	–	–	1	1	4	–	1
	D	–	–	–	–	1	–	–	–	–	–	2	–	–	–	–	–
	E	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Marginal staining	**A**	31	31	31	31	31	27	26	23	20	18	16	11	16	10	6	3
	B	–	–	–	–	–	1	–	2	6	5	5	8	5	8	7	8
	C	–	–	–	–	–	–	–	–	–	–	–	1	1	2	–	–
	D	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	E	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Postoperative sensitivity	**A**	31	31	31	31	29	28	26	25	24	23	21	19	20	18	13	10
	B	–	–	–	–	2	–	–	–	2	–	–	1	2	2	–	1
	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	D	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	E	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Recurrence of caries	**A**	31	31	31	31	31	28	26	25	26	23	21	20	22	20	13	11
	B	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	D	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	E	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Abbreviations: *ER-D*, etch-and-rinse, dry dentin; *ER-M*, etch-and-rinse, moist dentin; *SE-et*, self-etch with selective enamel etching; *SET*, self-etch without selective enamel etching. FDI criteria: A (very good); B (good); C (sufficient/satisfactory); D (unsatisfactory); and E (poor)

Table 5 Number of evaluated restorations for each experimental group classified according to the modified US Public Health Service (USPHS) criteria[40,41] in different follow-up times (6, 18, and 36 months)

USPHS criteria		Baseline				6 months				18 months				36 months			
		ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET
Retention	**A**	31	31	31	31	30	28	25	25	26	23	19	20	22	20	13	11
	B	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–
	C	–	–	–	–	1	3	5	6	3	6	10	9	5	7	14	16
Marginal adaptation	**A**	31	31	31	31	30	28	26	25	23	18	13	18	18	15	6	2
	B	–	–	–	–	–	–	–	–	3	5	6	2	4	5	7	9
	C	–	–	–	–	1	–	–	–	–	–	2	–	–	–	–	–
Marginal staining	**A**	31	31	31	31	31	27	26	23	25	22	19	18	21	18	7	5
	B	–	–	–	–	–	1	–	2	1	1	2	2	1	2	6	6
	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Postoperative sensitivity	**A**	31	31	31	31	29	28	26	25	24	23	21	19	20	18	13	10
	B	–	–	–	–	2	–	–	–	2	–	–	1	2	2	–	1
	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Recurrence of caries	**A**	31	31	31	31	31	28	26	25	26	23	21	20	22	20	13	11
	B	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	C	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Abbreviations: *ER-D*, etch-and-rinse, dry dentin; *ER-M*, etch-and-rinse, moist dentin; *SE-et*, self-etch with selective enamel etching; *SET*, self-etch without selective enamel etching. USPHS criteria: A (Alpha); B (Bravo); and C (Charlie)

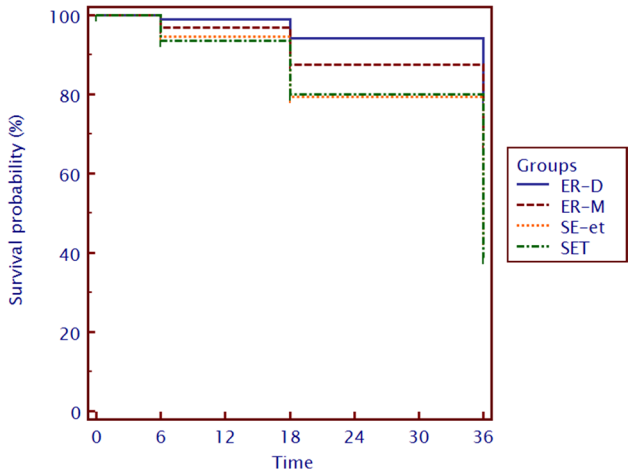

Fig. 2 Kaplan–Meier curve showing significant differences among the cumulative probability of the primary endpoint

Table 6 Retention loss hazard ratio (95% confidence interval) for pairwise comparison of different groups

Pairwise comparison	Hazard ratio (95% CI)
SET vs. ER-D	3.44 (1.88 to 6.20)*
SET vs. ER-M	3.22 (1.76 to 5.87)*
SET vs. SE-et	1.06 (0.58 to 1.95)
SE-et vs. ER-D	1.93 (1.06 to 3.53)*
SE-et vs. ER-M	1.81 (0.99 to 3.3)
ER-M vs. ER-D	1.77 (0.97 to 3.24)

*Groups significantly different

Marginal adaptation

After 36 months of clinical evaluation, 57 restorations (ER-D = 16, ER-M = 18, SE-et = 12, SET = 11) showed some marginal discrepancies based on FDI criteria (Table 4); 25 restorations (ER-D = 4, ER-M = 5, SE-et = 7, SET = 9) had marginal discrepancies based on USPHS criteria (Table 5). We found no statistically significant difference among groups after 36 months' recall time for either criterion ($p < 0.52$).

Other parameters

No restoration exhibited clinical problems related to recurrence of caries at 36 months of clinical evaluation based on FDI or USPHS criteria. After 36 months, only five restorations showed postoperative sensitivity (ER-D = 2, ER-M = 2, SET = 1) based on either criterion ($p > 0.93$; Tables 4 and 5).

Discussion

The results of the present study showed that after 36-month follow-up, a large number of restorations were lost, regardless of the adhesive strategy used for the evaluated universal adhesive. The retention rates for Xeno Select universal adhesive were around 80.0% for ER (ER-D = 83.9%, ER-M = 77.4%) and 52% for SE (SE-et = 54.9%, SET = 48.4%), which seemed low when compared with other 36-month clinical evaluations of universal adhesives in NCCLs [27, 28, 42]. For example, in Perdigão et al.'s [28] and Ruschel et al.'s [42] studies, the retention rates were 100% for restorations in the ER group and 93% for restorations in the SE group after 36-month recall. Several factors could be responsible for the low retention rates observed in our study.

As described in the "Introduction" section, universal adhesives are similar to simplified SE adhesives [8, 9]. Therefore, the former can be classified according to their pH and depth of interaction with dentin [43]. Most commercially available universal adhesives are classified as mild or ultra-mild adhesives [11]. Usually, ultra-mild universal adhesives have been clinically evaluated [27, 28, 42]. However, according to the manufacturer's description, Xeno Select can be classified as an intermediately strong adhesive (pH 1.0–2.0, manufacturer instructions) [44], due

Table 7 Number of evaluated restorations for each experimental group according to the Semiquantitative Score (SQUACE)[39] in different follow-up times (6, 18, and 36 months)

Classification	6 months				18 months				36 months			
	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET	ER-D	ER-M	SE-et	SET
Less than 10%	17	18	15	12	11	11	5	10	10	6	5	3
Between 10 and 30%	13	9	9	11	16	11	14	5	15	14	10	9
Between 31 and 50%	1	1	2	2	1	3	2	7	1	4	2	3
Statistical analysis*	A	A	A	A	B	B	B	B	C	C	C	C

Abbreviations: *ER-D*, etch-and-rinse, dry dentin; *ER-M*, etch-and-rinse, moist dentin; *SE-et*, self-etch with selective enamel etching; *SET*, self-etch without selective enamel etching

*Different letters indicate significant differences between groups for each time (Kruskal–Wallis, $p > 0.05$)

to the similarity of its composition with its predecessor, Xeno [45].

Low bond strength and high nanoleakage to dentin have been observed when intermediately strong universal adhesives, such as Xeno Select, were compared with ultra-mild universal adhesives, regardless of the adhesive strategy [12, 46, 47]. Unpolymerized, acidic, and aggressive monomers are able to continue demineralizing dentin even after polymerization in more acidic simplified adhesives [48, 49]. Hydrolysis of the ester bond from the acid monomer results in production of a strong phosphoric acid [48, 49] independent of adhesive strategy when compared to milder adhesives. Consequently, more collagen fibrils might have been exposed, causing greater degradation of adhesive interfaces in our long-term evaluation [45, 48].

Although several functional monomers can be used to formulate universal adhesives, the most notable is 10-MDP [8, 9]. A majority of clinical studies have evaluated 10-MDP-containing universal adhesives [27, 28, 42]. Data related to 10-MDP-free adhesives are scarce. Xeno Select is an MDP-free universal adhesive. According to the manufacturer, instead of 10-MDP, Xeno Select contains two acidic monomers in its composition [50]. The first one is an "inverse" functionalized phosphoric acid ester very similar to dipentaerythritol pentaacrylate–phosphoric acid monomer (PENTA), which can establish a covalent bond with the Ca in dentin and enamel [51]. The second alternative to MDP is acryloyl amino alkyl sulfonic acid. There is sufficient in vitro evidence that these monomers initially bind to the Ca in hydroxyapatite, but the Ca salt produced by this chemical interaction should also be stable [7]. This does not occur, however, as the monomers debond in an aqueous environment [52, 53]. In the SE strategy, even selective enamel etching did not significantly improve clinical performance.

Although both adhesive strategies showed poor results for Xeno Select when compared with the literature, we observed a noticeably higher retention rate for the ER groups when compared to the SE groups (80.65% vs. 51.7%). In the SE mode, clinical performance only depended on the chemical bonding produced by the functional monomers with the dental substrates [54]; however, in the ER mode, it may be related to the fact that after phosphoric acid etching, micromechanical bonding and the production of a better-impregnated hybrid layer compared to the SE mode [54] accounted for the higher retention rate of the universal adhesive we tested. This led us to partially reject our primary null hypothesis.

It is worth mentioning that keeping the dentin dry or moist after phosphoric acid application did not influence the clinical performance of Xeno Select. Actually, as an SE adhesive, it is important that water be added [11]. In the composition of universal adhesives, water is an important ingredient because it ionizes the acidic groups. This allows the formation of hydronium ions, which etch hydroxyapatite [55]. The water content of universal adhesives is strongly related to their pH because it is essential to ionize the acidic functional monomers in order to make the self-etching procedure possible [55, 56]. Although the manufacturer does not specify the amount of water in Xeno Select, it is possible to speculate that it was enough to guarantee good bonding performance, mainly when dentin was kept dry. These results agree with clinical results for universal adhesives when applied in the ER mode in dry or moist dentin [29, 57].

Although retention rate by itself is enough to demonstrate Xeno Select's poor clinical performance, we evaluated other parameters such as marginal adaptation and discoloration as well. Regardless of the bonding strategy used, we observed significant deterioration of marginal adaptation and increased marginal staining after 36 months of clinical use that was usually greater than in previous literature [27, 28, 42].

We found marginal discrepancies in 54.8% of restorations in ER groups and 40.3% of restorations in the SE group after 36 months of clinical evaluation using FDI criteria. On the other hand, for example, in Loguercio et al.'s [29] study, 23.9% of the restorations in ER groups and 31.8% of the restorations in SE groups presented some marginal discrepancy when using the same criteria. We found marginal discrepancy in 54.8% of ER group restorations and 40.3% of SE group restorations using the same criteria. The same rationale seems to apply when evaluating marginal discoloration. As previously described, Loguercio et al. [29] evaluated an MDP-containing universal adhesive, rather than an MDP-free universal adhesive as evaluated in this study.

Although the comparison between criteria used for evaluation is not the main objective of the present study, it is important to be evaluated by both criteria, mainly because, several clinical trials continue to use USPHS [27, 28, 42], instead of FDI criteria, which is considered more sensitive than the USPHS-modified criteria to small variations in the clinical outcomes of NCCLs [58]. For example, while 30.5% of ER restorations and 63.5% of SE restorations showed some degree of marginal discrepancy after 36 months of clinical service when we evaluated them for USPHS criteria, Atalay et al. [27] showed that only 13.5% of ER group restorations and 22.5% of SE group restorations presented some kind of marginal discrepancy after 36 months using the same criteria. Although we evaluated an MDP-free universal adhesive, Atalay et al. [27] used an MDP-containing universal adhesive.

Interestingly, we observed no significant differences in marginal adaptation or marginal discoloration when we compared the ER and SE groups after 36 months of clinical evaluation, which leads us to accept our second and third null hypotheses. This seems to stand in contrast to previous studies [27, 28, 42]. However, a closer view of the different

studies showed the same direction. For example, Ruschell et al. [28] showed higher and significant difference in the degree of marginal adaptation for SE (30%) when compared to ER (5.7%) groups for one of the universal adhesives evaluated. On the other side, in the present study, this significant difference was not observed, since 54.8% and 40.3% of restorations in the ER and SE groups, respectively, after 36 months of clinical evaluation showed some signs of marginal discrepancies. We observed that both studies showed that ER strategy showed lower marginal discrepancies when compared to SE strategy; instead, no significant difference was observed in the present study. Probably, the high number of restoration losses in the present study when compared to the previous one [27, 28, 42] may have prevented a better analysis of these criteria, because only a small number of restorations were available for clinical evaluation. Also, no restorations showed signs of postoperative sensitivity or recurrence of caries, regardless of the technique applied, which leads us to accept our fourth and fifth null hypotheses.

It is worth mentioning that because the nature of universal adhesives as Xeno Select is intrinsically hydrophilic, different clinical approaches were developed to overcome the poor clinical performance [59]. For instance, the application of an additional hydrophobic layer or multiple coats of the same adhesive [60–62], previous conditioning with EDTA [63], and increasing the polymerization time [64] were some clinical approaches previously evaluated that improve the clinical behavior of one-step self-etch adhesives. Therefore, future clinical studies need to be conducted to compare the clinical performance of Xeno Select, mainly in the self-etch strategy, when associated with some of these clinical approaches.

Just like many other clinical trials, this one had some limitations. The study was conducted in a university setting, with all restorations placed in an ideal scenario by two well-calibrated and supervised operators. In this setting, only motivated patients with a low caries risk were included. Therefore, future clinical studies need to be conducted to compare the universal adhesives in a practice-based study. Clinical trials have greater value when published after long-term follow-ups. The absence of studies using universal adhesives with follow-up periods longer than 36 months could justify the follow-up period we used for restorations. However, the large number of failures in this long-term follow-up, which maintained a tendency that was already seen in the short-term results [44], made us interrupt this clinical trial following the recommendation of our university's ethics committee. Patients will continue to be monitored, and restorations that eventually have problems will be replaced, but this study's data will no longer be used as an evaluation criterion for the Xeno Select adhesive.

Based on the previous literature, we conclude that the overall high failure rate observed for this adhesive material is not new [44, 65, 66]. Therefore, to protect patients and dentists, a discussion about the necessity and importance of clinical trials is urgently needed before launching new dental materials on the market, as recently suggested by van Dijken et al. [66].

Conclusion

The 36-month clinical behavior of Xeno Select universal adhesive depends on the bonding strategy used. However, the overall clinical performance of the universal adhesive was poor, mainly in SE application.

Author contribution Marcos O. Barceleiro: clinical evaluator, paper revisor, and study director. Leticia S. Lopes: performed restorative procedures. Chane Tardem: dental assistant, clinical evaluator, and paper writer. Fernanda S. Calazans: performed restorative procedures. Thalita P. Matos: dental assistant and paper writer. Alessandra Reis and Abraham Lincoln Calixto: paper revisor. Alessandro D. Loguercio: clinical evaluator, paper revisor, and study director.

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Declarations

Ethical approval This study was approved by the Fluminense Federal University ethics committee (protocol 800.273/14). All procedures performed in this study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all participants prior to starting the treatment.

Conflict of interest The authors declare no competing interests.

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