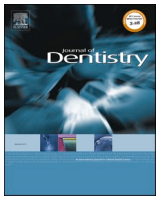
Journal of Dentistry 168 (2026) 106587

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent



Clinical evaluation of composite restorations placed on dimethyl sulfoxide-treated cervical carious lesions: a 36-month randomized double-blind controlled trial

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ARTICLE INFO

Keywords:
DMSO
Dimethyl sulfoxide
Clinical trial
Carious cervical
Adhesive
Bond
Primer

ABSTRACT

Objectives: To evaluate the effect of a novel restorative approach using dimethyl sulfoxide (DMSO) as a cavity pretreatment on the material fracture and retention (primary outcome) of direct composite fillings placed on cervical carious lesions (CCLs).
Methods: 45 patients presenting CCLs were screened and randomized into two groups containing 37 caries lesions/group: an untreated control (20 patients) and a DMSO-treated (25 patients) group. Following a parallel-study design, two calibrated operators placed 74 ($n = 37$) composite fillings (Filtek Z350XT, 3 M ESPE) using a 2-step etch-and-rinse adhesive (Single Bond 2, 3 M ESPE). After baseline assessments (7 days), fillings were evaluated at 12-, 24- and 36-month follow-ups according to the FDI criteria (fracture/retention, marginal staining, marginal adaptation, postoperative sensitivity and caries recurrence). For statistical analysis, Chi-Square and Cochran's Q tests were used ($\alpha = 0.05$) following the Bonferroni correction.
Results: DMSO had significant effects on the clinical performance of composite fillings placed on CCLs according to the FDI criteria ($p < 0.05$). Success rates after 36 months of untreated and DMSO-treated cavities were 65 % and 89 %, respectively, with a 70 % lower risk of failure when using DMSO. DMSO significantly reduced post-operative sensitivity and marginal staining and improved retention rates after 36 months ($p < 0.05$).
Conclusions: Long-term clinical performance of composite fillings using simplified etch-and-rinse adhesives can be optimized by employing DMSO as a cavity pretreatment.
Clinical significance: The use of DMSO can be a simple clinical approach to improve post-operative sensitivity of composite fillings, reduce risk of failures and extend service life by producing more stable composite-tooth interfaces.

1. Introduction

Over the past decades, composite restorations have become the first choice of direct restorative treatment in dentistry worldwide [1,2]. Although composite restorations may bear acceptable long-term survival rates (*i.e.,* annual failure rates below 2 % [3–5]), substantial time and effort are still spent by practitioners to replace clinically failed restorations [6]. University- and practitioner-generated clinical data [7]

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https://doi.org/10.1016/j.jdent.2026.106587
Received 18 December 2025; Received in revised form 15 February 2026; Accepted 25 February 2026
Available online 26 February 2026

show that replacement of defective restorations account for over 55 % of all clinical work in restorative dentistry, with an increasing trend for the coming years [7]. To date, the main cause of failures remain secondary caries and/or fractures and composite's choice alone does not necessarily seem to guarantee higher survival rates [8].

Parafunctional habits, socioeconomic factors and operator's experience play a crucial role in the clinical longevity of composite restorations. In this context, bonding methacrylate-based resins to tooth structures consist of clinically technique-sensitive procedures reaching different clinical outcomes [9]. Such complexity is reflected by failures requiring additional clinical interventions within 11 % of restorations after just 1 year of placement, 20 % after 3 years and 50 % after 10 years of composite placement [6]. Differences in the success rate of composite restorations widely range from 44–98 %, presenting survival rates from 23–97 % [8] after long-term clinical function. Annual failures also show considerable variation ranging from 0.08–6.3 % [8]. Hence, the recently acknowledgement of operator's experience as a risk factor corroborates its importance in the success of restorative treatments [8]. Determining how dentists deal with the complexity of bonding protocols and handle such technique-sensitive clinical procedures on different pathologically altered bonding substrates in the oral cavity (*i.e.,* sclerotic [10], eroded [11] or carious [12] dentin) is critical for the lifespan of resin-bonded restorations. Impaired penetration of methacrylate-based monomers [12,13], compromised collagen structure [14], variability in dentin's mineralization and moisture levels [13] present significant challenges in dental adhesion to altered bonding substrates [10–12]. Such morphological changes not only further increase the technique sensitivity for clinical bonding procedures, but they can also substantially compromise the longevity of composite restorations [13]. This is relevant within the current context of clinical placement of composite restorations, since caries remains the most prevalent oral disease, affecting >2 billion people globally [15] and costing billions to both public and private sectors [16]. More importantly, the high biological cost of frequent restoration replacements charges an inestimable toll on patients' oral health by increasing the likelihood of premature tooth loss [17].

Means to avert teeth from descending into the so-called "restorative death spiral" [17] are attainable only thorough preventive measures and by extending the longevity of existing dental restorations. Bonding resin-based materials to carious dentin indeed remains challenging, despite all progress in dental adhesion over the years [12,18,19]. Resin bonding effectiveness is inversely proportional to the degree of caries progression [18], typically producing inferior outcomes on carious than sound dentin [19], irrespective of adhesive type. Over the past decade, a solid body of *in vitro* evidence [20] has grown to support the use of dimethyl sulfoxide (DMSO) to improve resin bonding to both sound [21–30] or eroded [31] dentin. Successful long-term outcomes were obtained either by incorporating DMSO into commoner blends [32–34] or as a separate pretreatment [21–30]. While *in vitro* long-term bond--strength studies may somehow correlate with clinical outcomes [35,36] (*i.e.,* considering marginal discoloration [37], but not necessarily for retention rates or marginal integrity [37]), direct extrapolation of *in vitro* findings to clinical applications is not feasible or recommended [35].

Therefore, the aim of this double-blind, randomized controlled clinical trial was to determine the clinical performance of a simplified etch-and-rinse bonding resin bonded to DMSO-treated caries-affected cavities. The central research question was stipulated as: can cavity pretreatments (untreated or DMSO-treated) affect the long-term clinical performance of composite restorations placed on caries-affected cavities using etch-and-rinse resins? The tested null hypotheses were that during a 3-year follow-up period 10 % (v/v) aqueous DMSO used as a cavity pretreatment would have no effect: (*i*) on the material fracture and retention, as the primary outcome, of composite restorations bonded with a two-step etch-and-rinse adhesive to cervical carious lesions or (*ii*) on the clinical performance assessed by the FDI criteria, as the secondary outcome.

2. Material and methods

2.1. Ethical approval and protocol registration

The local ethics committee reviewed and approved the study protocol (# 010122). The trial was registered at ClinicalTrials.gov (NCT05090085) on October 22, 2021 and conducted in accordance with the Declaration of Helsinki, ensuring adherence to established ethical and scientific standards. The local ethics committee also approved an amendment extending the investigation period to three years. Written informed consent was obtained from all participants prior to treatment initiation. The study design and reports complied with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [38].

2.2. Trial design, settings and location of data collection

This was a randomized, double-blind (patient and examiner), controlled clinical trial conducted at the Conservative Dentistry Department clinic of Horus University, New Damietta, Egypt, from January 2022 to January 2025. The participants were informed about the study's nature and objectives, but they were blinded towards the received treatments under evaluation.

2.3. Sample size calculation

The sample size was calculated based on a previous study [39], in which the success rate of resin composite cervical carious restorations was 73 % for a simplified adhesive following the etch-and-rinse mode after 36 months. By implementing a two tailed Z test for difference between two independent proportions with an alpha level of 5 % and a power of 80 %. The statistical unit was set as tooth affected by cervical carious lesions and the minimum sample size needed was 30 restorations per group in order to detect a difference of 25 %. Sample size was increased by 25 % to compensate for possible dropouts, reaching 37 teeth per group ($n = 37$). Sample size was performed using G*Power version 3.1.9.2 for windows.

2.4. Participant recruitment

Participants were recruited from patients seeking treatment at the dental clinics of the local university. Eligible individuals were invited to enroll in the study in the order in which they presented for the screening session, thereby forming a convenience sample. No advertisements were used for participant recruitment. Two calibrated dentists/researchers recruited the patients and selected the teeth. The calibration process began before the screening sessions. All participants were informed about the study's nature and objectives, but they were unaware of what tooth received the specific treatments. Written informed consent was obtained from all participants before starting treatment.

2.5. Eligibility criteria and baseline characteristics of the selected teeth

All participants underwent a comprehensive examination by two trained operators to confirm eligibility. Clinical assessments were performed using a mouth mirror, explorer and periodontal probe. Eligible participants were required to be in good general health according to the American Society of Anesthesiologists (ASA) Physical Status Classification System, restricted to ASA I (healthy individuals) or ASA II (patients with mild systemic disease without significant functional limitations) [40]. Additional inclusion criteria were: age ≥18 years, acceptable oral hygiene, as determined by the Simplified Oral Hygiene Index (OHI-S) [41], and a minimum of 20 teeth in occlusion. Features of teeth to be filled were evaluated before the placement of composite restorations. This included observing and recording features such as the presence of antagonists, attrition facets and relevant sociodemographic information for each patient. Smokers were not included in this study.

Characteristics of research subjects and the distribution of cervical carious lesions are shown in Table 1.

The characteristics of the cervical carious lesions were assessed. Lesion dimensions (height and width, in mm) and lesion geometry were evaluated using a UNC 15 periodontal probe and profile photographs taken at a 135° angle and recorded [42]. Among such teeth, comparable cervical carious lesions with similar in size, shape, depth and in need of restorative treatment. Table 2 summarizes inclusion and exclusion criteria. Eligible cervical carious lesions could be located on any teeth in either arch, provided they were non-retentive, deeper than 1 mm after caries removal, involving enamel and dentin without periodontal mobility. Participants with signs of periodontitis (probing pocket depth >4 mm with bleeding during probing and loss of clinical attachment higher than 3 mm in more than four teeth) [43], extremely poor oral hygiene [41], heavy bruxism habits (severe masticatory muscle pain, temporomandibular joint pain, or extreme tooth wear) [44], continuous use of medication, patients undergoing bleaching treatments, pregnant women and presence of orthodontic devices or removable prosthesis were excluded from the study. Pulp vitality was assessed through the cold test. Non-vital teeth and non-carious lesions were excluded. Cavities with depths higher than 3 mm after caries removal were filled, but discarded from this study and replaced. Pre-operative sensitivity was documented when it was spontaneous and in response to an air-stream stimulus 2 cm away from the tooth for 5 s. Following such examinations, 28 patients were excluded and 45 were recruited after accepting the terms of the research (Fig. 1). All subjects were given oral hygiene instructions before performing the operative treatment.

2.6. Randomization sequence generation, allocation concealment and blinding

Randomization was carried out using a free software available at http://www.random.org by a researcher who was not involved in any other phases of the study. Group assignments were recorded on cards and placed in sequentially numbered, opaque and sealed envelopes. The allocation was disclosed by opening the envelope immediately before the restorative procedure, ensuring concealment of the random sequence and preventing selection bias. Evaluators, who did not participate in the restorative treatment, remained blinded to the allocation assignments, ensuring unbiased outcome assessment. Patients were also unaware of the materials used in their restorative treatments, characterizing the study as double-blind. However, blinding of the operators was not feasible due to the substantial differences in bonding protocols.

Table 1
Demographic distribution and characteristics of research subjects (gender, teeth and age).

Gender distribution	*Number of subjects*		
	Untreated (Control)	DMSO	Row total (RT)
Male	7 35.0 % RT 35.0 % CT	13 65.0 % RT 52.0 % CT	20 (44.4 %)
Female	13 52.0 % RT 65.0 % CT	12 48.0 % RT 48.0 % CT	25 (55.6 %)
Column total (CT)	20 (44.4 %)	25 (55.6 %) $p = 0.2595$	45
Tooth distribution	*Number of teeth*		
	Untreated (Control)	DMSO	Row total (RT)
Maxillary anterior teeth	23 62.2 % RT 53.5 % CT	20 54.1 % RT 46.5 % CT	43 (58.1 %)
Maxillary premolars	3 8.1 % RT 25.0 % CT	9 24.3 % RT 75.0 % CT	12 (16.2 %)
Mandibular anterior teeth	2 5.4 % RT 50.0 % CT	2 5.4 % RT 50.0 % CT	4 (5.4 %)
Mandibular premolars	9 24.3 % RT 60.0 % CT	6 16.2 % RT 40.0 % CT	15 (20.3 %)
Column total (CT)	37 (50.0 %)	37 (50.0 %) $p = 0.2828$	74
Age (years)	Untreated (Control)	DMSO	Average
	28.1 ± 7.3	28.6 ± 6.6 $p = 0.740$	28.35 ± 6.9

Table 2
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients with cervical carious lesions deeper than 1 mm after preparation Age ≥18 years Good general health (ASA-I or II) Co-operative patients approved to participate in the study Acceptable oral hygiene (OHI-S) Vital asymptomatic teeth Favourable occlusion (minimum of 20 teeth) Occlusal contact with antagonist teeth	Absence of cervical carious lesions Presence of non-carious cervical lesions Cavities with depths higher than 3 mm after preparation Smoking Xerostomia Heavy bruxism habits Patients undergoing bleaching treatments Inability to return for recall appointments Fractured or visibly cracked teeth Current desensitizing therapy, including desensitizing dentifrices or other over-the-counter products Long-term use of anti-inflammatory analgesic or psychotropic drugs Pregnancy or breast-feeding Allergies to resin-based restorative materials Orthodontic treatment Abutment teeth for fixed or removable prostheses Teeth or supporting structures with any symptomatic pathology Existing periodontal disease or periodontal surgery within the previous three months

2.7. Operator's calibration

The same two-experienced dentists/researchers involved in the participants' selection performed the restorative procedures. The study director placed two composite restorations (one for the control and for the DMSO-treated group), allowing the identification of all steps involved in the restorative procedure. Then, the two operators placed four restorations from each group for calibration, under the supervision of the study director in a clinical setting. Composite restoration's deficiencies were discussed with the operators before starting the study. Details that could potentially influence the quality of the composite restorations, such as caries removal, DMSO-pretreatment application, bonding procedures, composite layering, light-curing technique, finishing and polishing, among others, were thoroughly discussed and calibrated. Any discrepancies in the restorative procedures were identified and settled with the operators before the start of the trial. The calibrated operators filled all teeth under the study director's supervision.

2.8. Clinical intervention: restorative procedures

Teeth to be filled received a preliminary dental prophylaxis with pumice and water using a rubber cup before the restorative procedure. Using a shade guide, the proper composite shade was determined. Before placing the rubber dam, local anesthesia was administered as necessary (Articaine–L, Alexandria Co, Egypt). Since the study was conducted on shallow or moderately deep cavities, caries removal followed the "selective removal to firm dentin" concept [45], also known as selective caries removal [46,47]. Caries lesions were completely

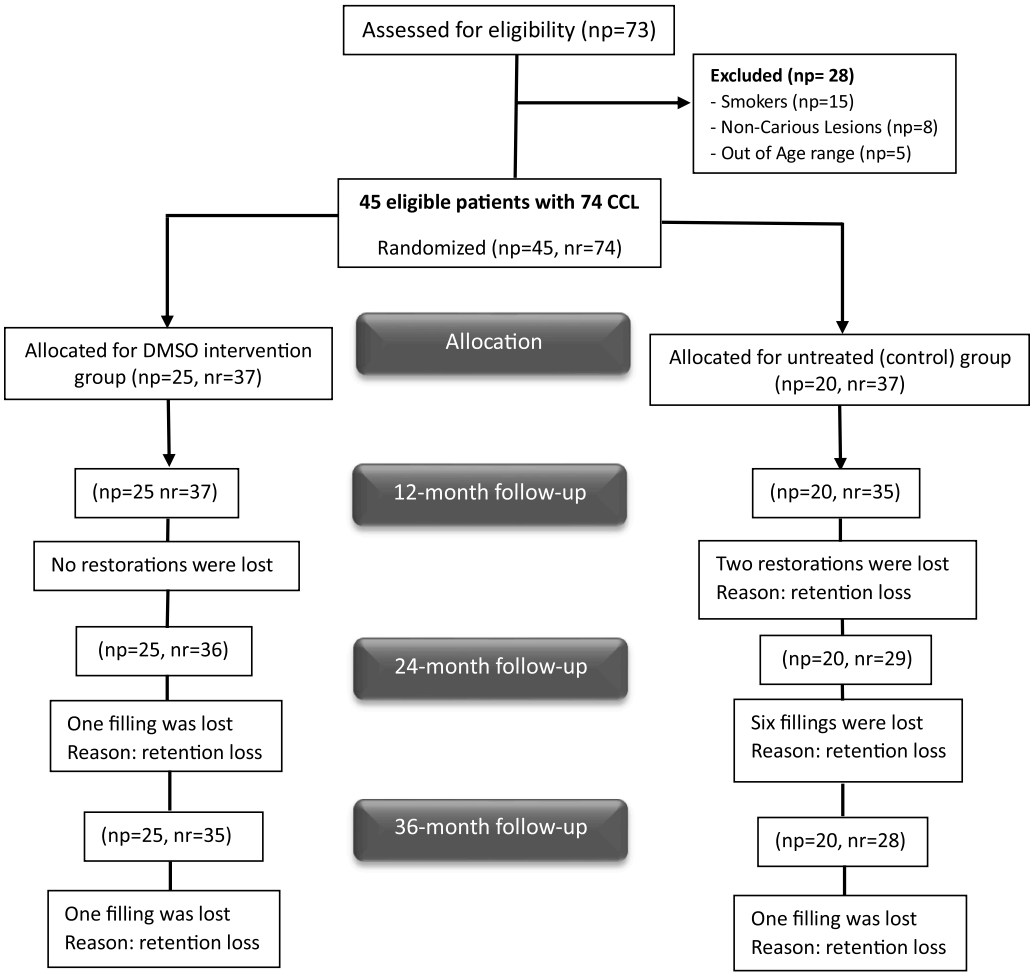

Fig. 1. CONSORT flow diagram in the different phases of the study design.
Abbreviations: *np = number of patients, *nr = number of restorations, CCL= cervical carious lesions.

removed from external walls (exposing hard-firm dental tissues) and at axial walls a firm "leathery" surface was exposed. Caries removal was performed by a round diamond point (BR-31, Mani, Japan), forming non-retentive cavity walls. Following the guidelines of the American Dental Association (ADA) [48], operators did not prepare any additional retentions or bevels within cavities.

A two-step etch-and-rinse bonding resin (Adper Single bond 2, 3 M ESPE, St. Paul, MN, USA) was selected following two groups: (*i*) control group (untreated) and (*ii*) 10 % (v/v) DMSO in distilled water for 60 s. 10 % (v/v) DMSO was selected based on the premise that it would offer similar benefits at lower concentrations [30] as the traditionally employed 50 % (v/v) solution [21,23,27,31,49], but with lower cytotoxicity. Furthermore, Aaqel and colleagues [50] investigated the cytotoxicity of DMSO concentrations up to 10 % and found no adverse effects on biocompatibility when incorporated into hydrophobic resin. A previous clinical trial [51] investigated the effect of 1 % DMSO/H_2O and found no adverse effect on vitality of non-carious cervical lesions and have significant improvement on marginal staining. Unpublished pilot data showed that even DMSO at 50 % (v/v) has a minor role in cytotoxic responses of odontoblast-like cells (ISO 7405 [52] standard testing for trans-dentinal cytotoxicity). Since DMSO is generally accepted as nontoxic below 10 % (v/v), the lower concentration was selected for this study. Both enamel and dentin were etched with 37 % phosphoric acid (Scotchbond Universal Etchant, 3 M ESPE) for 30 s and 15 s, respectively. After etching, cavities were rinsed for 15 s and air-dried for 5 s to remove excess water. Dentin was kept slightly moist before bonding procedures, following the wet-bonding technique for etch-and-rinse adhesives [53]. For the control group, the adhesive application followed the manufacturer's recommendations. The bonding agent was applied over all cavity walls in two separate coats of 15 s each using disposable cavity brushes (Kerr Applicators, Kerr Dental, USA) and air-dried for 15 s to remove excess solvents after each coat. Passive application (*i.e.,* light manual pressure) was used over enamel margins [54], while vigorous active application was employed over dentin surfaces [55]. Light-curing was performed for 20 s at 1200 mW/cm^2 (Bluephase 20i, Ivoclar Vivadent, Schaan, Liechtenstein) to ensure adequate polymerization. For the intervention group, an aqueous 10 % DMSO (v/v) pretreatment solution was utilized. After etching, cavity surfaces were rinsed for 15 s, air-dried for 5 s and pretreated with the DMSO solution for 60 s using a disposable cavity brush. DMSO application was performed actively [23]. An air-stream was gently applied for 10 s to evaporate the excess of the pretreating solution using an air-syringe at a distance of 10 cm, ensuring that cavity surfaces remained slightly moist without any DMSO-water pooling. The adhesive system was applied as described for the control group. The operators restored the cervical tooth anatomy by applying three increments of a nanofilled composite (Filtek Z350 XT Universal Restorative, 3 M ESPE, St. Paul, MN, USA). Each increment was light-cured for 20 s at 1200 mW/cm^2 (Bluephase 20i, Ivoclar Vivadent, Schaan, Liechtenstein). A radiometer (Bluephase meter II, Ivoclar Vivadent, Schaan, Liechtenstein) was employed to verify the irradiance for every set of three restorations. Composite restorations were finished immediately with fine and extra-fine diamond burs (#3195F and #3195FF) and aluminum oxide polishers (OneGloss, Shofu Japan) and polishing spirals (Soft-lex

Pre-Polishing; Soft-lex Diamond Polishing, 3 M ESPE) under water-cooling. Detailed information about the composition, application mode and batch number of used restorative materials are shown in Table 3.

2.9. Clinical evaluation

Two blinded, experienced and calibrated dentists, who were not involved in the restorative procedures, conducted the clinical evaluations. During evaluations, all parameters were documented on standardized report forms, which were forwarded to the research staff after each session to ensure that examiners remained blinded to group assignments throughout the follow-up visits. Patients were also blinded to their group assignments. For a proper evaluation, examiners performed a dental prophylaxis with pumice and water over the teeth's surface before the evaluation. Clinical evaluation was performed using a dental explorer and an intraoral mirror. Composite restorations were evaluated using two sets of criteria available at the beginning of the trial: the FDI criteria [48,56]. For calibration of the evaluation criteria, the examiners reviewed 10 photographs, representative of each score from FDI criteria [48]. An inter- and intra-examiner agreement of at least 85 % was required before initiating the assessments [57]. Intraoral digital photographs were taken of all composite restorations at the different time periods and a paper case report was used at each recall time to ensure examiners were kept blind to previous evaluations during the follow-up recalls. Assessments were performed immediately after the restorative procedure at baseline (7 days) and at 12, 24 and 36 months of clinical service. Only the clinically relevant parameters of adhesive performance were considered. The primary outcome was material fracture and retention, while the secondary outcomes included marginal staining, marginal adaptation, post-operative sensitivity and secondary caries. Spontaneous post-operative sensitivity (POS) was assessed at baseline (7 days after the restorative procedures) by asking patients whether they experienced any pain since the restorative procedure through the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) self-completed by the patient. The VAS scale consisted of a 10 cm linear scale with the words "no pain" and "unbearable pain" at opposing ends from each other. The NRS consisted of five verbal points (0 = none and 4 = severe), with 0 meaning no pain and 4 meaning severe pain. Pulp vitality was assessed by the cold test. Variables were classified according to the FDI criteria as clinically very good, clinically good, clinically sufficient/satisfactory, clinically unsatisfactory but repairable and clinically poor (replacement required) [48,56]. Both examiners evaluated all composite restorations once and independently. When there was disagreement during such assessments, the examiners reached a consensus before dismissing the patient. Failed composite restorations due to retention loss or secondary caries, which could not be repaired were replaced with new restorations [48]. Such composite restorations were excluded from the study for further evaluation. Repairs were exclusively carried out on restorations ranked as clinically satisfactory according to the FDI criteria. Repaired restorations (*i.e.,* due to chipping, delamination or secondary caries) were considered as relative failures, monitored and evaluated as an integral part of the study for further evaluations [56].

Table 3
Materials' composition and application modes.

Material	Composition	Application mode
Etching agent, Scotchbond Universal Etchant (3 M ESPE) Batch# N7523	Water, 34 % phosphoric acid, synthetic amorphous fumed silica, polyethylene glycol, aluminium oxide (pH 0.6)	1. Apply etchant for 30 s on enamel and 15 s on dentin 2. Rinse for 15 s
2-step etch-and-rinse adhesive, Adper Single Bond 2 (3 M ESPE) Batch# NA82584	Ethanol, bis-GMA, silane-treated silica, HEMA, copolymer of acrylic and itaconic acids, GDMA, UDMA, water (<5 %), DPI	1. Air-dry for 5 s to remove excess water 2. Dentin was kept slight moist 3. Apply the adhesive actively for 20 s in 2 separate coats 4. Gentle air-dry for 15 s to remove solvents after each coat 5. Light-curing for 20 s (Bluephase 20i, 1200 mW/cm^2)
Nanofilled composite, Filtek Z350 XT Universal Restorative (3 M ESPE) Batch# NA81717	Silane treated ceramic, bis-GMA, bis-EMA, UDMA, silane treated silica, silane treated zirconia, PEGDMA TEGDMA Inorganic filler loading about 72.5 % by weight (55.6 % by volume). Non-agglomerated/non-aggregated 20 nm silica filler. Non-agglomerated/non-aggregated 4 to 11 nm zirconia filler. Aggregated zirconia/silica clusters.	1. Placed in increments of maximum 2 mm 2. Light-curing for 20 s (Bluephase 20i, 1200 mW/cm^2)
Pretreatment solution, DMSO	Distilled water, 10 % (v/v) DMSO	1. After etching, rinsing and drying, apply DMSO solution actively for 60 s 2. Air-dry for 10 s keeping cavities partially moist, but avoiding pooling of solvents (water and/or DMSO)

Abbreviations: HEMA = 2-hydroxyethyl methacrylate; bis-GMA = bis-phenol diglycidylmethacrylate; GDMA = Glycerol 1,3-dimethacrylate; UDMA = diurethane dimethacrylate, DPI = Diphenyliodonium hexafluorophosphate; TEGDMA= Triethylene glycol dimethacrylat; PEGDMA=Polyethylene Glycol Dimethacrylate and bis-EMA= bisphenol A ethoxylated dimethacrylate; DMSO = Dimethyl sulfoxide.

2.10. Statistical analysis

The statistician was blinded to group allocation. Statistical analysis followed an intention-to-treat approach, as recommended by CONSORT [38]. Data were analyzed using Medcalc software, version 22 for windows (MedCalc Software Ltd, Ostend, Belgium). Descriptive statistics were applied to summarize the distributions of the FDI criteria as frequency and percentage. Inter-examiner agreement was assessed using Cohen's kappa statistics. Intergroup comparisons between interventions (Control *vs.* DMSO) were performed using Chi-Square test with statistical significance levels were set at 5 % ($\alpha = 0.05$). Intragroup comparisons within each intervention (Control or DMSO) were performed using the Cochran's Q test after FDI scores were dichotomized into two categories: success (clinically very good, clinically good, and clinically sufficient/satisfactory) and failure (clinically unsatisfactory, but repairable or clinically poor requiring replacement) [58] with significance level was set at 0.0083, after Bonferroni correction. Relative risk was used to assess the clinical significance. Survival rates for at each follow-up (7 days, 12-, 24- and 36-month) were estimated using Kaplan-Meier analysis. Survival distributions were compared using the Log-rank test and Hazard ratios (HRs) with 95 % confidence intervals were also reported. The confidence limit was set at 95 % with 80 % power and all tests were two-tailed.

3. Results

Twenty-eight out of 73 patients examined for eligibility were not enrolled in the study (Fig. 1) for not fulfilling the inclusion criteria. Thus, a total of 45 subjects (20 males; 25 females) were selected. Seventy-four composite restorations were placed, totaling 37 restorations in each group ($n = 37$). Restorative procedures were performed according to the established protocol without any modifications. Table 1

presents the demographic distribution of participants' details and the characteristics of the treated lesions. The mean participant's age was 28.35 ± 6.9 years, without significant differences between control (28.1 ± 7.3 years) and DMSO (28.6 ± 6.6 years) groups ($p = 0.740$). No significant differences were observed between control (7 males; 13 females) and DMSO (13 males; 12 females) groups regarding gender distribution ($p = 0.2595$). Tooth distribution is shown in Table 1, without significant differences between groups ($p = 0.283$). All participants were assessed at baseline (7 days) and during the 12-, 24- and 36-month follow-ups, with a recall rate of 100 %. Inter-rater reliability between the two examiners was assessed using Cohen's kappa, yielding a coefficient of 0.8929 (95 % CI: 0.7714 to 1.0000), indicating an acceptable level of agreement.

3.1. Retention and fracture

According to the FDI criteria classification (Table 4), no significant differences in retention/fracture of composite restorations place on untreated (Control) or DMSO-treated cavities were observed at baseline (7 days; $p = 1.00$) or 12 months ($p = 0.1544$). Significant differences in retention/fracture were detected between untreated (Control) and the DMSO-treated group at 24 months ($p = 0.0134$*) or 36 months ($p = 0.0231$*). At 24 months of clinical service, 9 composite restorations were lost (Control: 8 [21.6 %], DMSO: 1 [2.7 %]). At 36 months, 1 additional restoration was lost from untreated (Control) cavities and 1 additional restoration was lost from DMSO-treated cavities, totaling 11 restorations lost (Control: 9 [24.3 %], DMSO: 2 [5.4 %]). The 36-month retention/fracture rates (95 % CI) were 35 % (22–51) for composite restorations placed on untreated (Control) cavities and 11 % (4–25) for DMSO-treated cavities (Table 5). The Kaplan-Meier analysis (Fig. 2) revealed significant differences between the cumulative probability of failure ($p = 0.0098$). Paired comparisons between the two groups, expressed as hazard ratios (HR), are detailed in Table 6. Significant differences were observed between untreated- and DMSO-treated

Table 5
Absolute risk (95 % CI) and relative risk (95 % CI) for clinical performance for both groups after 36 months.

	Absolute risk (95 % CI)	*Relative risk (95 % CI)*
Untreated (Control)	35 (22–51)	-
DMSO	11 (4–25)	0.3 (0.11–0.86)

Table 4
Number of evaluated composite restorations for each group classified according to the FDI criteria.

FDI	Follow-up	Control n(%)						DMSO n(%)						P value
		N	Success			Failure		N	Success			Failure		
			1	2	3	4	5		1	2	3	4	5	
Fracture and Retention	Baseline	37	37(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	1.0000
	12 months	37	35 (94.6)	0(0)	0(0)	0(0)	2(5.4)	37	37(100)	0(0)	0(0)	0(0)	0 (0)	0.1544
	24 months	37	29 (78.4)	0(0)	0(0)	0(0)	8 (21.6)	37	36 (97.3)	0(0)	0(0)	0(0)	1 (2.7)	0.0134*
	36 months	37	28 (75.7)	0(0)	0(0)	0(0)	9 (24.3)	37	35 (94.6)	0(0)	0(0)	0(0)	2 (5.4)	0.0231*
	P value	$p< 0.001$*						$p= 0.194$						
Marginal Integrity	Baseline	37	37(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	1.0000
	12 months	35	33 (94.3)	2 (5.7)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	0.1431
	24 months	29	26 (89.6)	1 (3.5)	2(6.9)	0(0)	0(0)	36	35 (97.2)	0(0)	1(2.8)	0(0)	0(0)	0.2806
	36 months	28	26 (92.8)	1 (3.6)	1(3.6)	0(0)	0(0)	35	35(100)	0(0)	0(0)	0(0)	0(0)	0.128
	P value	$p<0.001$*						$p= 0.194$						
Marginal Discoloration	Baseline	37	37(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	1.0000
	12 months	35	33 (94.3)	2 (5.7)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	0.1431
	24 months	29	18 (62.1)	0(0)	8 (27.6)	3 (10.3)	0(0)	36	33 (91.7)	0(0)	3(8.3)	0(0)	0(0)	0.0027*
	36 months	28	18 (64.3)	0(0)	6 (21.4)	4 (14.3)	0(0)	35	29 (82.9)	0(0)	4 (11.4)	2 (5.7)	0(0)	0.0977
	P value	$p<0.001$*						$p= 0.019$						
Postoperative Hypersensitivity	Baseline	37	27(73)	2 (5.4)	0(0)	8 (21.6)	0(0)	37	34 (91.9)	3 (8.1)	0(0)	0(0)	0(0)	0.0071*
	12 months	35	35(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	0.8137
	24 months	29	29(100)	0(0)	0(0)	0(0)	0(0)	36	36(100)	0(0)	0(0)	0(0)	0(0)	0.3853
	36 months	28	28(100)	0(0)	0(0)	0(0)	0(0)	35	35(100)	0(0)	0(0)	0(0)	0(0)	0.3778
	P value	p=0.001*						$p= 0.194$						
Secondary Caries	Baseline	37	37(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	1.0000
	12 months	35	35(100)	0(0)	0(0)	0(0)	0(0)	37	37(100)	0(0)	0(0)	0(0)	0(0)	0.8137
	24 months	29	29(100)	0(0)	0(0)	0(0)	0(0)	36	36(100)	0(0)	0(0)	0(0)	0(0)	0.3853
	36 months	28	28(100)	0(0)	0(0)	0(0)	0(0)	35	35(100)	0(0)	0(0)	0(0)	0(0)	0.3778
	P value	$p<0.001$*						$p= 0.194$						

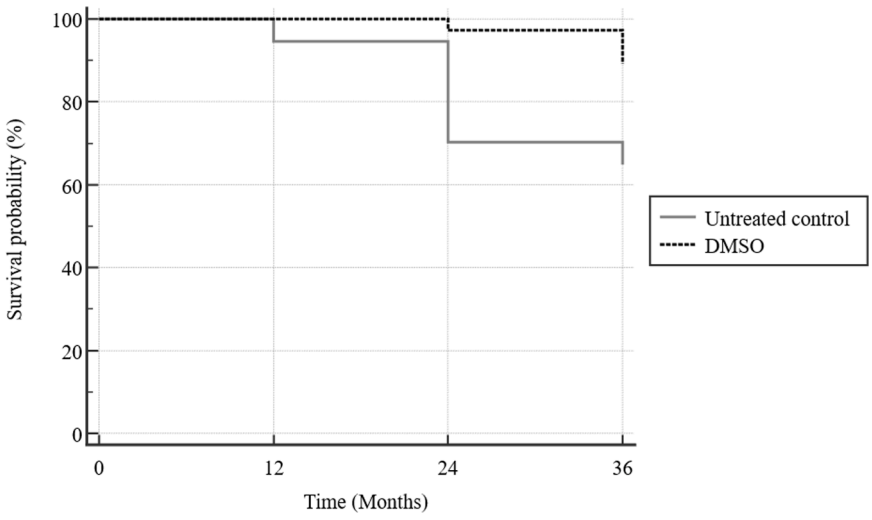

Fig. 2. Survival probability of composite fillings performed on untreated (Control) or DMSO-treated cervical carious lesions using a 2-step etch-and-rinse adhesive up to 36 months of clinical service.

Table 6
Retention loss hazard ratio (95 % confidence interval).

Pairwise comparison	Hazard ratio (95 % CI)
Untreated (Control) *vs.* DMSO	3.75 (1.37–10.24) *

* Indicates significant differences between groups.

cavities (HR 3.75; 95 % CI 1.37–10.24), indicating that untreated cavities were 3.75 times more likely to debond or fracture compared to DMSO-treated cavities.

3.2. Marginal integrity

According to the FDI criteria (Table 4), no significant differences in marginal integrity were observed between composite restorations placed on untreated (Control) or DMSO-treated cavities at baseline ($p = 1.00$), 12- ($p = 0.1431$), 24- ($p = 0.2806$) or 36-month ($p = 0.128$) follow-ups. Intragroup analysis showed significant deterioration over time for the control group ($p < 0.001$), which was not observed for DMSO-treated cavities. The latter exhibited a rather stable performance over the follow-ups without significant differences over time ($p = 0.194$).

3.3. Marginal discoloration

No significant differences in marginal discoloration, according to the FDI criteria (Table 4), were detected between composite restorations placed on untreated (Control) or DMSO-treated cavities at baseline (7 days) or 12-month follow-up ($p = 0.1431$). At the 24-month follow-up, 14 composite restorations exhibited marginal discoloration (Control: 11 [37.9 %], DMSO: 3 [8.3 %]). Composite restorations placed on DMSO-treated cavities presented significantly lower marginal discoloration compared to untreated (Control) cavities ($p = 0.0027$). At the 36-month follow-up, 16 restorations presented marginal discoloration, but no significant differences were observed between composite restorations placed on untreated (Control: 10 [35.7 %]) and DMSO-treated (6 [17.1 %]) cavities ($p = 0.0977$). Significant deterioration through time was identified for both treatments, more pronounced for untreated (Control) cavities ($p < 0.001$) than DMSO-treated cavities ($p = 0.019$).

3.3.1. Post-operative sensitivity (POS)

At baseline (7 days), 13 composite restorations (Control: 10 [27 %], DMSO: 3 [8.1 %]) exhibited post-operative sensitivity (POS) according to the FDI criteria. Composite restorations placed on DMSO-treated cavities presented significantly lower manifestation of POS compared to untreated (Control) cavities at baseline ($p = 0.0071$). No composite restorations showed POS at the remaining 12-, 24- or 36-month follow-ups (Table 4).

3.3.2. Secondary caries

No composite restorations presented recurrence of caries at baseline (7 days) or during any of the remaining follow-ups (12-, 24- or 36-month), regardless of cavity pretreatments (Table 4; $p > 0.05$).

4. Discussion

The present double-blind randomized controlled clinical trial is the first follow-up study assessing the effect of DMSO on the clinical performance of composite restorations placed on caries-affected cavities. Following previously published *in vitro* findings [20,21,30,22–29], demonstrating enhanced resin-dentin bonding after DMSO pretreatment, the present clinical results showed clear clinical improvements. The higher success rate observed for DMSO-treated cavities (89 %) compared with untreated cavities (65 %) after 36 months confirms that the tested restorative protocol effectively enhanced the durability of restorations bonded with a simplified etch-and-rinsed adhesive. This led to the rejection of the first null hypotheses.

Extending the service life of composite restorations benefits both patients and healthcare systems by reducing the need for frequent reinterventions [16] and minimizing the biological cost for patients [17]. In this respect, patient- and operator-related factors are of primary importance to determine the survival rates of direct restorations [8,59]. This is especially true given the technique sensitivity of current bonding procedures. Cervical carious lesions with limited enamel margins and non-retentive cavity geometry represent a demanding bonding scenario and are therefore ideal substrates for evaluating the effect of adhesive strategies on the clinical performance of direct composite restorations [60]. Adhesive selection can significantly influence the longevity of cervical composite restorations [61]. While simplified adhesives offer easier and faster application, they do not always result in superior clinical outcomes [9,62]. However, bonding agents with shorter application times have gained widespread popularity in the recent years [63]. This is reflected by the growing number of clinical studies assessing such type of bonding resins [63]. Two-step etch-and-rinse adhesives, such as the one used in this study, are often considered less durable than multi-step adhesive systems [9], especially in cervical regions [61,62].

Therefore, they provide an ideal model to test whether DMSO pre-treatments could compensate for their well-documented limitations suggested by previous *in vitro* studies [21–30]. Universal adhesives were intentionally not included in this study, due to insufficient *in vitro* data demonstrating DMSO-related benefits for such adhesives. Nonetheless, the clinical performance observed in this study is promising, particularly considering the struggle to successfully extrapolate *in vitro* findings to the clinical scenario [64].

Bridging the translational gap [64] in adhesive dentistry has been challenging [65–69]. Bonding protocols that perform exceptionally well *in vitro*, such as ethanol-wet bonding [65], chlorhexidine [66,67] or cross-linker agents [68], eventually fail to replicate their benefits *in vivo* [65–68]. This discrepancy is likely due to the complex environment in the oral cavity, where mechanical, thermal, enzymatic, bacterial, pH-induced and hydrolytic challenges are not easily replicated *in vitro*. Therefore, randomized clinical trials [70] remain essential to validate potential bonding improvements. Within this context, the present findings indicate that DMSO is a rare example of an *in vitro* strategy that translates effectively into extending the clinical durability of composite restorations. Based on the findings of this study, DMSO emerges as an exception to the frustrating often faced translational gap [64] in adhesive dentistry, opening new possibilities to extend the service life of methacrylate-based restorative procedures.

Robust long-term evidence, however, is still required before establishing clinical recommendations [69]. Adding an additional step to restorative protocols could only be justified if the benefits outweigh the required time and effort. In this study, DMSO significantly reduced marginal discoloration at the 24-month follow-up, which is considered a main reason for failures of cervical composite restorations [8]. Improvements in retention rates at both 24- and 36-month follow-ups also provides evidence that DMSO can indeed contributed to better clinical outcomes. Interestingly, the absence of significant differences between untreated and DMSO-treated groups regarding marginal discoloration at 36 months is likely due to the higher loss of composite restorations in the untreated group, which resulted in fewer composite restorations available for evaluation of marginal quality. Such composite restorations were accounted for retention loss rather than marginal discoloration. Longer clinical follow-ups could be valuable to clarify this observation.

Significant improvements in both marginal discoloration and post-operative sensitivity (POS) and the absence of significant differences between untreated and DMSO-treated groups considering marginal integrity or secondary caries led to partial rejection of the second null hypothesis. It is worth mentioning that the significant loss of marginal integrity over time for untreated cavities was not observed for DMSO-treated cavities. Although such deterioration differences may suggest initial signs of DMSO-related protective effects, the necessity of longer follow-ups to better understand the effect of DMSO on marginal integrity and secondary caries are evident. Nonetheless the selected observation period provided compelling evidence about the benefits of employing DMSO as part of restorative procedures. For instance, POS was significantly lower at baseline (7 days) with the use of DMSO. POS, frequently reported in cervical restorations ranging from 40 % [71] to 71 % [72], is often directly associated to restorative procedures, albeit it is not necessarily related to etching protocols (*e.g.* etch-and-rinse *vs.* self-etch adhesives) [73] on cervical lesions [62]. The peak of occurrence here was 7 days, as previously reported [71]. POS tends to disappear over time [71], which was also confirmed by the present study using the simplified etch-and-rinse adhesive. Critically, POS occurrence also signals for flaws attributed to inadequate dentin hybridization, incomplete wetting of dentin surfaces by the bonding resins, poor adhesive polymerization or marginal gaps, resulting from composite's shrinkage stresses. Such flaws can facilitate hydrodynamic movement within dentinal tubuli, transmit hydraulic pressure to odontoblastic processes and trigger painful sensitivity [74], according to Brännström's hydrodynamic theory [75]. Interestingly, significantly lower occurrences of marginal staining at earlier stages (*i.e.,* 24-month follow-up) and higher retention rates indicate that DMSO can enhance the lifespan of composite restorations. Furthermore, significant reductions in POS at baseline (7 days) for DMSO-treated cavities invariably links such service-life improvements to optimized and more stable resin-dentin interactions. DMSO has a unique ability to displace water molecules [23], which can substantially optimize interactions between methacrylate-based co-monomers of different hydrophilicities [21,22,24,29,33] to the inherently wet dentin substrate [22,27–29]. Additionally, lower technique sensitivity [27–29], higher monomer penetration [22] through better pre-stabilized collagen matrices [28], better wetting [27] and more efficient incorporation of cross-linking monomers within hybrid layers [28] likely contributed to enhanced clinical bonding effectiveness. It is reasonable to assume that DMSO produced more homogenous and durable hybrid layers *in vivo,* contributing to better clinical outcomes.

Beyond statistical significance, the magnitude of clinical benefits is an important determinant for clinical decision-making. The number needed to treat (NNT = 5.2) for the tested primary outcome (*i.e.,* retention rates) can help explain the nondeterministic notion of potentially employing DMSO as an effective pretreatment to extend the longevity of composite restorations. NNT allows quantification of the therapy's overall benefit in terms of the number of treated patients. The obtained NNT of 5.2 means that around 5 patients should be treated with DMSO, so one can benefit from it. This represents a favorable benefit-to-effort ratio and can be considered a modestly good NNT, given the simplicity, low cost, minimal risk and applicability of DMSO across a broad range of clinical situations [15]. Additionally, significantly lower Hazard ratio for failure (74 % reduction) reinforces the clinical relevance of employing DMSO to extend the service life of composite restorations.

Despite the strengths of this university-based study, certain limitations must be acknowledged. While the present generated clinical data is adequate to determine the ideal performance of material and new protocols, practice-based clinical studies would be more suitable to analyze their typical performance. Possible limitations of this study may include the lack of time constrains for restorative procedures performed in a university-based setting, without time-related issues observed in private practices. Convenience sampling was also a potential source of selection bias, albeit often used in long-term follow-up studies. Therefore, the results cannot be interpreted as valid for the general population, since this was a single-center study composed by subjects from a single region. Future studies should consider different communities and routine clinical practice based on less-than-ideal conditions. Different adhesive classes should also be included to verify the possibility of expanding the benefits of DMSO on caries-affected cavities to other classes of adhesives. Different forms of DMSO application, such as incorporation into bonding resins [33,34], should also be considered for further simplification.

5. Conclusion

Simplification of clinical restorative procedures remain necessary; however, more elaborated approaches can further improve the service life of composite restorations. The proposed DMSO pretreatment protocol seems to be an appealing option to extend the durability of composite restorations placed on caries-affected cavities when simplified etch-and-rinse bonding resins are employed. Collectively, reductions in post-operative sensitivity and marginal discoloration, along with increased retention rates, substantiate the use of DMSO pretreatments for improving the bonding of methacrylate-based materials to caries-affected substrates.

Ethical policy and institutional review board statement

Faculty of Dentistry, Horus University in Egypt, Research Ethics committee approved and gave the code: #010122

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Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study design was approved by the internal review board of Horus University, Egypt (reference: #010122) in a joint supervision agreement with the University of Turku, Finland. The study was registered prior to commencement at ClinicalTrials.gov, Trial Number: (NCT05090085).

Informed consent

Written informed consent was obtained from all individual patients included in this study before starting the clinical procedures.

CRediT authorship contribution statement

Omar Abdelaziz Ismail: Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Thiago Henrique Scarabello Stape:** Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Omar Shaalan:** Formal analysis, Investigation, Writing – original draft, Data curation. **Noha Taymour:** Resources. **Ibrahim El-Dossoky Basha:** Investigation, Supervision. **Walaa Mohamed Ahmed Alsamoully:** Methodology, Validation, Investigation, Supervision. **Arzu Tezvergil-Mutluay:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by funding from the Finnish Cultural Foundation (#00250411).

Data availability

All data used in this publication are available within the article itself. No additional data repositories are required for access.

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