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ORIGINAL ARTICLE

Six-month 3-dimensional Cone-Beam Computed Tomography Assessment of Periapical Healing After Conventional Endodontic Treatment with 3 Different Endodontic Sealers: A Comparative Prospective Clinical Trial

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ABSTRACT

Objective: To evaluate periapical healing at a 6-month follow-up after single-visit endodontic treatment using 3 commonly employed sealers—zinc oxide–eugenol (C-Gross), epoxy resin-based (AH Plus), and calcium silicate-based (Bio-C Sealer)—assessed through 3-dimensional cone-beam computed tomography (CBCT) volumetric analysis.

Methods: A comparative, parallel, non-randomised, double-blinded clinical design was used. Seventy-five patients with pulp necrosis and chronic apical periodontitis were enrolled; 70 completed follow-up (AH Plus: n = 25; Bio-C: n = 23; C-Gross: n = 22). Treatments were performed by 10 supervised postgraduate operators following a standardised protocol. Preoperative and 6-month CBCT scans were segmented by 2 calibrated, blinded radiologists (κ = 0.90). Lesion volumes were obtained using manual boundary tracing and automated 3D reconstruction. Intragroup and intergroup comparisons were evaluated using non-parametric statistics.

Results: All 3 sealers showed significant intragroup reductions in lesion volume over 6 months ($P < .001$). Median volumes decreased from 81.0 to 15.0 mm^3 (AH Plus), 63.0 to 12.0 mm^3 (Bio-C), and 36.0 to 4.5 mm^3 (C-Gross). Percentage reductions were similarly high across groups (median 79.7%-84.9%). No significant differences were observed among sealers for absolute volumetric change ($P = .096$) or percentage reduction ($P = .912$).

Conclusions: Periapical healing was comparable across AH Plus: n = 25; Bio-C: n = 23; C-Gross: n = 22. When disinfection, 3-dimensional obturation, and coronal sealing are optimally achieved, sealer composition has minimal influence on tissue repair. Healing appears primarily host-driven, governed by inflammatory resolution and bone remodelling rather than sealer-derived bioactivity.

Keywords: Cone-beam computed tomography, endodontic treatment outcomes, periapical healing, root canal sealer, volumetric analysis

HIGHLIGHTS

- Cone-beam computed tomography volumetric analysis detected substantial lesion reduction that would be underestimated with conventional periapical radiography.
- Calcium silicate–based sealers did not outperform epoxy resin or zinc oxide–eugenol sealers, contradicting the widespread belief that "bioactivity" enhances biological healing.
- Periapical healing appears primarily host-driven, with sealer composition exerting minimal influence when disinfection and obturation are performed effectively.

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INTRODUCTION

The primary goal of endodontic therapy is to prevent or halt pulpal disease and to maintain or restore periapical (PA) health. Large-scale studies report conventional endodontic treatment (CET) success rates of 78%-97%, depending on the initial diagnosis and the presence of apical periodontitis (AP).[1,2] Accordingly, AP remains a critical prognostic factor influencing CET outcomes.

The development and persistence of AP depend on antigenic stimuli, including bacterial by-products and toxins from the root canal system.[3] The antigen-antibody interactions in PA tissues indicate an immunopathological basis for AP.[3] The AP develops from the release of pro-inflammatory cytokines, which favour the expression of certain molecules associated with bone metabolism, such as the activator of the nuclear-kB receptor factor (RANK), the RANK-ligand (RANKL), osteoprotegerin, the receptor of the parathyroid hormone 1 (PTHR1), and the expression of the *Runx2* gene.[3,4] These factors increase osteoclastic activity with osteolytic results at the PA bone tissue. Radiographically, AP presents as radiolucent/hypodense lesions.[3,4]

The CET combines chemo-mechanical preparation with 3-dimensional (3D) obturation to remove organic debris, bacteria and bacterial by-products, enclosing the infection and promoting optimal conditions for PA healing.[5] When the antigenic challenge is eliminated, inflammation subsides, allowing osteoblastic activity and periodontal ligament reorganisation.[5] Persistent microbial or antigenic residues maintain T-lymphocyte and macrophage activation, driving osteoclastic resorption via interleukin-1 beta (IL-1β) and Transforming growth factor-beta (TNF-β).[3,4] Effective chemo-mechanical disinfection and sealing thus promote PA regeneration and tissue homeostasis.

The CET depends on root canal obturation to create a 3D hermetic seal that entombs residual microorganisms.[6] Gutta-percha (GP) is the most widely used obturation material, but its lack of adhesion to dentine necessitates a cement sealer to fill the interface and prevent micro-leakage, which could compromise treatment success.[6]

Endodontic sealers should possess biocompatibility, antibacterial activity, and appropriate physicochemical properties, including setting time, flow, radiopacity, solubility, and dimensional stability.[7] Sealers may influence bone deposition and remineralisation, potentially affecting apical healing through leachates at the apical foramen.[7]

Zinc oxide–eugenol (ZOE)-based sealers were introduced by Grossman in 1936 for use with GP.[7] With a long history of clinical and scientific use, ZOE cements remain the gold standard for evaluating and developing new endodontic sealers.[8]

Epoxy resin–based sealers (ERBS) were first introduced by Schröeder in 1954, composed of epoxy resin and bisphenol.[7] Later formulations improved physicochemical properties, including flow, solubility, dimensional stability, sealing ability, radiopacity, dentine adhesion, cytotoxicity, and antimicrobial activity, establishing ERBS as the endodontic standard.[9]

Bio-ceramics, an emerging category of endodontic sealers, were introduced to the field of endodontics in the early 1990s.[10] A recent mapping review on dental biomaterials revealed that bio-ceramics were a research emphasis from 2007 to 2019.[11] The most widely used bio-ceramic endodontic sealers are calcium silicate-based cements (CSCs). In addition to displaying excellent physicochemical attributes, CSCs exhibit high biocompatibility and bioactivity.[10] The bioactivity of these materials refers to their ability to form hydroxyapatite nodules when exposed to calcium- and phosphate-rich tissue fluids, conferring osteo-inductive and osteoconductive potential.[10,12] This may suggest accelerated post-endodontic PA healing. Although CSCs show promising clinical outcomes, further controlled trials are needed to provide high-level evidence for their use in endodontics.[10]

Although conventional 2-dimensional PA radiographs remain the standard for assessing post-endodontic healing, their limitations—including anatomical noise, geometric distortion, temporal perspective, and compression of 3-dimensional structures—can compromise accurate detection and evaluation of PA lesions.[13]

Cone-beam computed tomography (CBCT) is a 3D imaging modality that overcomes the limitations of 2-dimensional radiography and provides information not available with PA.[14] Compared with PA, CBCT demonstrates higher sensitivity and negative predictive value for detecting PA lesions, using histopathology as the reference standard.[14] Precise hypodensity volumes can also be measured and validated by integrating CBCT data with volume-rendering software.[14,15]

A recent systematic review—the highest level of scientific evidence—comprised 9 clinical trials assessing PA healing after CET with different endodontic sealers. Notably, all studies relied on 2-dimensional imaging to evaluate the healing process.[8] Consequently, current methods for assessing PA healing may be suboptimal, since the 2-dimensional nature of PA radiographs limits the understanding of the relationship between endodontic sealers and PA healing.

The present 6-month prospective clinical trial aims to comparatively evaluate post-endodontic PA healing in patients with pulp necrosis and chronic AP using 3 representative endodontic sealers, namely ZOE-based sealers (C-Gross), ERBS (AH Plus), and CSCs (Bio-C Sealer), by employing a 3D-CBCT volumetric approach.

MATERIAL AND METHODS

Ethical Clearance and Protocol Registration

The bioethics committee of the University Colegios de Colombia (UNICOC), Bogota, Colombia approved this prospective comparative clinical trial under Resolution No. 9-10-2022-5, Acta 40 (Date: October 19, 2022). The study protocol was registered in the ClinicalTrials.gov Protocol Registration and Results System (NCT06482593). All procedures adhered to the ethical guidelines for research involving human participants established by the Colombian Ministry of Health (Resolution 8430 of 1993) and complied with international standards for human experimentation outlined in the Declaration of Helsinki. Written informed consent, detailing the nature of the study as well as its potential benefits and risks, was obtained from all participants prior to enrolment.

Sample Size Calculation

G*Power 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used to estimate the sample size. Using a one-way ANOVA with a fixed effect ($\alpha = 0.05$, $1-\beta = 0.95$, $f = 0.05$), the calculation indicated that 20 patients per group were required. To account not only for potential dropouts but also for inter-individual clinical

variability and to ensure adequate statistical power for subgroup analyses, the target sample size was increased to 25 patients per group. Only 1 tooth per patient was included.

Study Groups

Group 1/control (n = 25): ZOE-based sealer (C-Gross; Prodont, Bogota, Colombia), Group 2 (n = 25): ERBS (AH Plus; Dentsply DeTrey, Konstanz, Germany), Group 3 (n = 25): CSCs (Bio-C Sealer; Angelus, Londrina, Brazil).

Patient Selection

Patients referred to the Department of Endodontics, University Colegios de Colombia (UNICOC), Bogota, Colombia, who needed CET were invited to participate in this prospective clinical trial.

Initial Inclusion Criteria

Patients classified as ASA I–II by the American Society of Anaesthetists, aged 18-60, requiring a single conventional endodontic treatment (CET) in a tooth with a single root and canal, were included. Diagnosis of pulp necrosis with asymptomatic (chronic) AP was confirmed by thermal (Hygienic Endo-Ice Green; Coltene Whaledent) and electrical (Digitest®; Parkell, USA) pulp sensitivity testing, and initial digital PA radiography verified the presence of a radiolucent endodontic lesion.

Exclusion Criteria

Exclusion criteria comprised teeth with combined endodontic–periodontal lesions, sinus tracts, history of dental trauma, calcified canals, severe curvatures, immature roots (open apex), radicular fractures, or developmental anomalies (e.g., dens evaginatus, dens invaginatus). Pregnant or lactating women, smokers, symptomatic patients, and those who had taken analgesics 12-24 hours before treatment were also excluded. Additionally, lesions involving adjacent teeth, cases with material extrusion, or procedural complications during CET (perforation, ledge formation, or broken instruments) were excluded from the trial.

Cone-Beam Computed Tomography Inclusion Criteria

Only patients meeting the initial inclusion criteria underwent CBCT. CBCT scans were acquired using a ProMax 3D Classic (Planmeca Group, Helsinki, Finland) at 90 kV and 12 mA, with a 5 × 5 cm field of view, 75 µm voxel size, and 14-second exposure. Scans were archived and analysed using Romexis software (Planmeca Group, Helsinki, Finland). Teeth with hypodense PA lesions scoring ≥3 on the CBCT PA index (CBCT-PAI),[16] not involving adjacent teeth and without buccal or lingual cortical plate compromise, were included in the trial.

Study Design

This study employed a comparative, parallel, non-randomised, double-blinded clinical trial design. The patient and the radiologists who assessed the CBCT scans in terms of CBCT inclusion criteria and calculated the 3D volumes preoperatively and at the 6-month follow-up were blinded to the process. Ten students (treating operators) in the final year of a 2-year full-time postgraduate endodontic training programme at University Colegios de Colombia (UNICOC), Bogota, Colombia, were responsible for verifying the initial inclusion criteria and performing the CETs following a standardised protocol, under the supervision of an experienced endodontist. The treating operators were not blinded. A non-probabilistic, consecutive recruitment design was adopted to ensure inclusion of all eligible patients within the study period, with sequential allocation to 1 of 3 experimental groups until 25 participants were enrolled in each group. This clinical trial included 75 patients who met both the initial and CBCT inclusion criteria.

Standardised Treatment Protocol

Initially, the treating operators (under supervision) conducted a comprehensive anamnesis together with clinical and digital PA examinations to obtain a complete dental history and establish an accurate endodontic diagnosis. Patients fulfilling the preliminary inclusion criteria subsequently underwent CBCT imaging. All CBCT scans were evaluated by a single experienced radiologist in the axial, sagittal, and coronal planes to confirm compliance with the CBCT-specific inclusion criteria. The treatment protocol was reviewed and approved by all participants before CBCT acquisition.

The CETs were performed in a single visit. Teeth were anaesthetised with Newcaina 2% + epinephrine 1:80 000 (New-stetic, Antioquia, Colombia). All the CETs were performed under single-tooth rubber dam isolation. Removal of caries and existing defective/failed restoration was performed. The Endo Access Kit (Dentsply Maillefer, Ballaigues, Switzerland) was used to prepare the access cavities. Initially, the pulp chamber was rinsed with 5% sodium hypochlorite (NaOCl) (ENZOHIP 5, Prodont Scientific, Bogota, Colombia). Apical patency was checked using a size 10K file (Dentsply Sirona Endodontics). Working length was determined using an apex locator (Root ZX II, J Morita, Kyoto, Japan) set to 0.5 mm and confirmed with digital PA. Before root canal shaping, a glide path with the Proglider File (Dentsply Maillefer) was performed. Root canal shaping was carried out using the WaveOne© Gold reciprocating system (Dentsply Maillefer, Ballaigues, Switzerland), following the manufacturer's recommendations. The treating operator and the supervisor selected the master apical file (Small (20.07), Primary (25.07), Medium (35.06), and Large (45.05)) based on the apical diameter of the root canal in each particular case. The choice of master apical file size was guided by clinical criteria, including assessment of apical anatomy, tactile feedback during file progression, canal curvature, and adequate irrigant penetration to the apical third, with the operator determining the apical diameter necessary to achieve effective cleaning and disinfection while maintaining apical integrity and avoiding procedural errors. It should be noted that, of the 75 included teeth, 10 canals were instrumented up to a Medium (35.06) master apical file, and the remaining canals up to a Large (45.05) master apical file. No teeth were left instrumented with the Small (20.07) or Primary (25.07) master apical files. Approximately 20–25 mL of NaOCl was used per canal. As final irrigants, 1 mL of 17% ethylenediaminetetraacetic acid (EDTA) (Laboratorios Eufar S.A., Bogota, Colombia) was applied for 1 minute, followed by 5 mL of distilled water.

Root canals were irrigated with 5 mL of 5% NaOCl (ENZOHIP 5, Prodont Scientific, Bogota, Colombia) between each instrumentation cycle. Approximately 20-25 mL of NaOCl was used for each canal. As final irrigants, 1 mL of 17% ethylenediaminetetraacetic acid (EDTA) (Laboratorios Eufar S.A, Bogota, Colombia) was applied for 1 minute, followed by 5 mL of distilled water. The NaOCl was activated once using ultrasonic activation (Ultra X ultrasonic activator, Eighteeth, Changzhou, China) for a period of 60 seconds during the irrigation protocol. The irrigation protocol was conducted using a Monoject syringe with a 30-gauge needle placed 2 mm short of the working length. Canal patency was achieved by passing a size 10 K file

(Dentsply Sirona Endodontics), 0.5 mm beyond the pre-established working length, after each instrumentation cycle.

Following biomechanical preparation, the root canal was dried using sterile paper points (Dentsply Maillefer, Ballaigues, Switzerland) matching the taper of the specific master apical file (primary, medium or large). Likewise, the master GP point cone (WaveOne® Gold GP Master Cones, Dentsply Maillefer, Ballaigues, Switzerland) was selected to match the taper and size of the final rotary NiTi instrument. The apical extent of the master cone was confirmed by a digital radiograph. Teeth were obturated according to the allocated groups. Group I: C-Gross, Group II: AH Plus and Group III: Bio-C Sealer. In groups 1 and 2, the sealers were mixed according to the manufacturer's specifications. Root canals were coated with the respective sealer using the master GP point. In group 3, the sealer was applied directly into the apical third. The syringe tip was inserted 2-3 mm short of the working length, and the sealer was injected retrogradely while retracting the syringe to ensure complete canal obturation.

The master GP point was then placed in position, followed by a lateral compaction technique using ISO size 15 accessory GP points to achieve a tight and sealed fill. After obturation, residual sealer on the pulp chamber was carefully removed, followed by a rinse with 70% isopropyl alcohol for 15-30 seconds to dissolve and inactivate any remaining eugenol, thereby minimising its inhibitory effect on resin polymerisation. Immediately after completion of CET, the root canal was coronally sealed with composite resin (Filtek Z350, 3M ESPE, USA). In teeth requiring intraradicular post rehabilitation, post cementation was performed by a prosthodontic specialist within 15 days of endodontic treatment.

Outcome Assessment

Each patient underwent 2 CBCT scans—preoperatively and at 6 months post-treatment—using identical imaging parameters. The 3D volumes preoperatively and at follow-up were similarly calculated with Romexis software (Planmeca Group, Helsinki, Finland). Lesions were initially identified in the axial plane, and their boundaries were manually delineated at 1-mm intervals using the Manual Segmentation tool in the annotations panel. The zoom function was used exclusively to improve visualisation of anatomical details and lesion margins, without altering image resolution or measurement calibration. This procedure was repeated across all relevant slices to fully outline the lesion. A 3-dimensional reconstruction was then generated using the Create Region function, which automatically calculated the lesion volume. Data were analysed by 2 experienced endodontic radiologists who were not involved in the treatment protocol. Before the study, both observers underwent calibration training to standardise the segmentation procedure. Inter-observer agreement for PA lesion volumes was excellent (Cohen's $\kappa = 0.90$, $P < .05$) (Figure 1). Representative images showing the measured lesions at baseline and at 6 months for each of the 3 sealer groups are presented (Figure 2).

Statistical Analysis

Data were analysed using R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). Baseline demographic variables, including age and gender, were compared across the 3 sealer groups. Age was analysed using the Kruskal–Wallis test, while gender distribution was assessed with the Chi-square test. Baseline (PRE) and 6-month (POST) volumetric measurements were summarised using both mean (SD) and median (Q1-Q3). Normality was assessed using the Shapiro–Wilk test; as this assumption was not met, non-parametric methods were applied. Intra-group differences (PRE vs. POST) were evaluated using the Wilcoxon signed-rank test. Inter-group comparisons among the sealers (AH Plus, Bio-C Sealer and ZOE) were performed using the Kruskal–Wallis test, considering both the absolute volumetric change (ΔVol) and the percentage reduction. When indicated, pairwise post-hoc comparisons were conducted using Dunn's test with Bonferroni correction. A P value < .05 was considered statistically significant.

RESULTS

Of 405 patients screened over 1 year, 75 met the inclusion criteria. One Bio-C Sealer case experienced sealer extrusion, and 1 C-Gross case showed PA lesion exacerbation 2 months post-treatment (requiring extraction).

Three participants were lost to the 6-month follow-up, leaving 70 patients for analysis (Group I: n = 22; Group II: n = 25; Group III: n = 23) (Figure 3).

Table 1 summarises the baseline demographic characteristics of the participants according to age and gender. The mean age was 48.0 years for the AH Plus group, 49.3 years for the Bio-C Sealer group, and 44.2 years for the zinc oxide group, with no statistically significant differences observed among groups ($\chi^2 = 2.10$; $P = .35$). Gender distribution was also comparable across groups ($\chi^2 = 4.05$; $P = .132$), with 56% of participants in the AH Plus group, 39.1% in the Bio-C Sealer group, and 27.3% in the zinc oxide group being male.

Table 2 summarises the initial (PRE) and 6-month (POST) lesion volumes for each sealer group, expressed as mean (SD) and median (Q1-Q3). All 3 sealers demonstrated a significant intragroup reduction in lesion volume over the 6 months. In the AH Plus group, the median volume decreased from 81.0 mm^3 to 15.0 mm^3 ($P < .001$). Bio-C Sealer showed a comparable reduction, with median values decreasing from 63.0 mm^3 to 12.0 mm^3 ($P < .001$). The C-Gross group also exhibited a marked reduction, from 36.0 mm^3 to 4.5 mm^3 ($P < .001$). Together, these findings indicate a consistent and statistically significant decrease in lesion volume within each sealer group.

Table 3 and Figure 4 summarise the percentage reduction in lesion volume for each sealer group, reported as mean (SD) and median (Q1-Q3). All 3 groups showed similarly high reductions, with median values ranging from 79.65% to 84.91%. These descriptive findings indicate that the extent of volumetric reduction was comparable across the 3 sealers.

No significant differences were observed between the sealers for either the absolute volumetric change (ΔVol; Kruskal–Wallis, $\chi^2 = 4.681$, $df = 2$, $P = .096$) or the percentage reduction ($\chi^2 = 0.185$, $df = 2$, $P = .912$). Dunn's post-hoc comparisons with Bonferroni correction revealed no significant pairwise differences for either ΔVol or percentage reduction (Table 4).

Teeth were grouped according to sealer type and tooth category (anteriors, premolars, and molars) for a subsequent descriptive analysis. Across all subgroups, apical lesion volumes decreased from baseline (PRE) to follow-up (POST). The corresponding volumetric data and percentage reductions are summarised in Table 5, providing

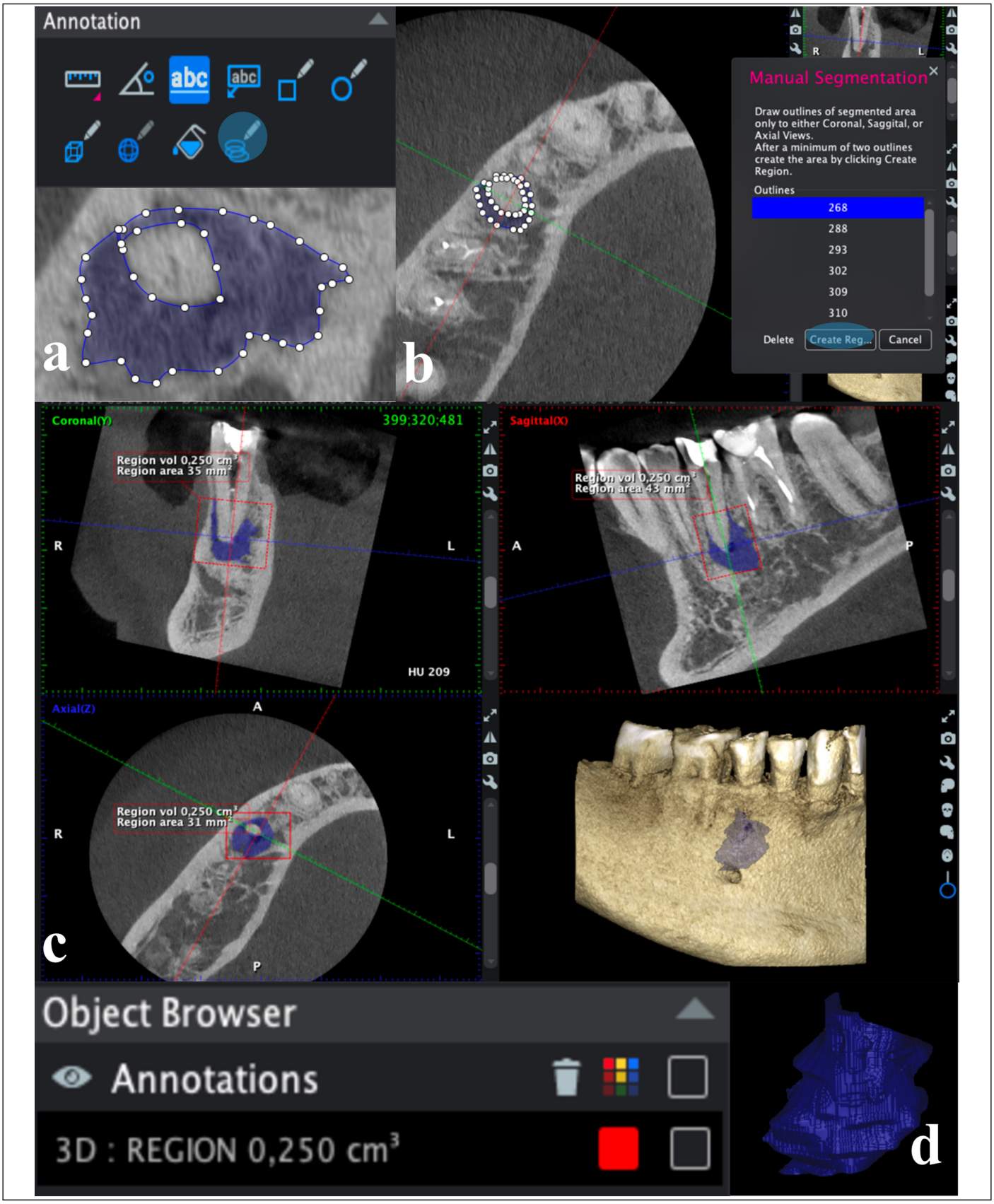


Figure 1. Segmentation and volumetric analysis of periapical lesions. (a) Axial-plane delineation of the lesion using the Manual Segmentation tool in Romexis. (b) Sequential outlining at 1-mm intervals across contiguous slices to capture the full lesion extent. (c) Multiplanar reconstructions (coronal, sagittal, and axial) showing the completed segmentation and the automatically calculated lesion volume. (d) Three-dimensional rendering of the segmented lesion generated using the Create Region function.

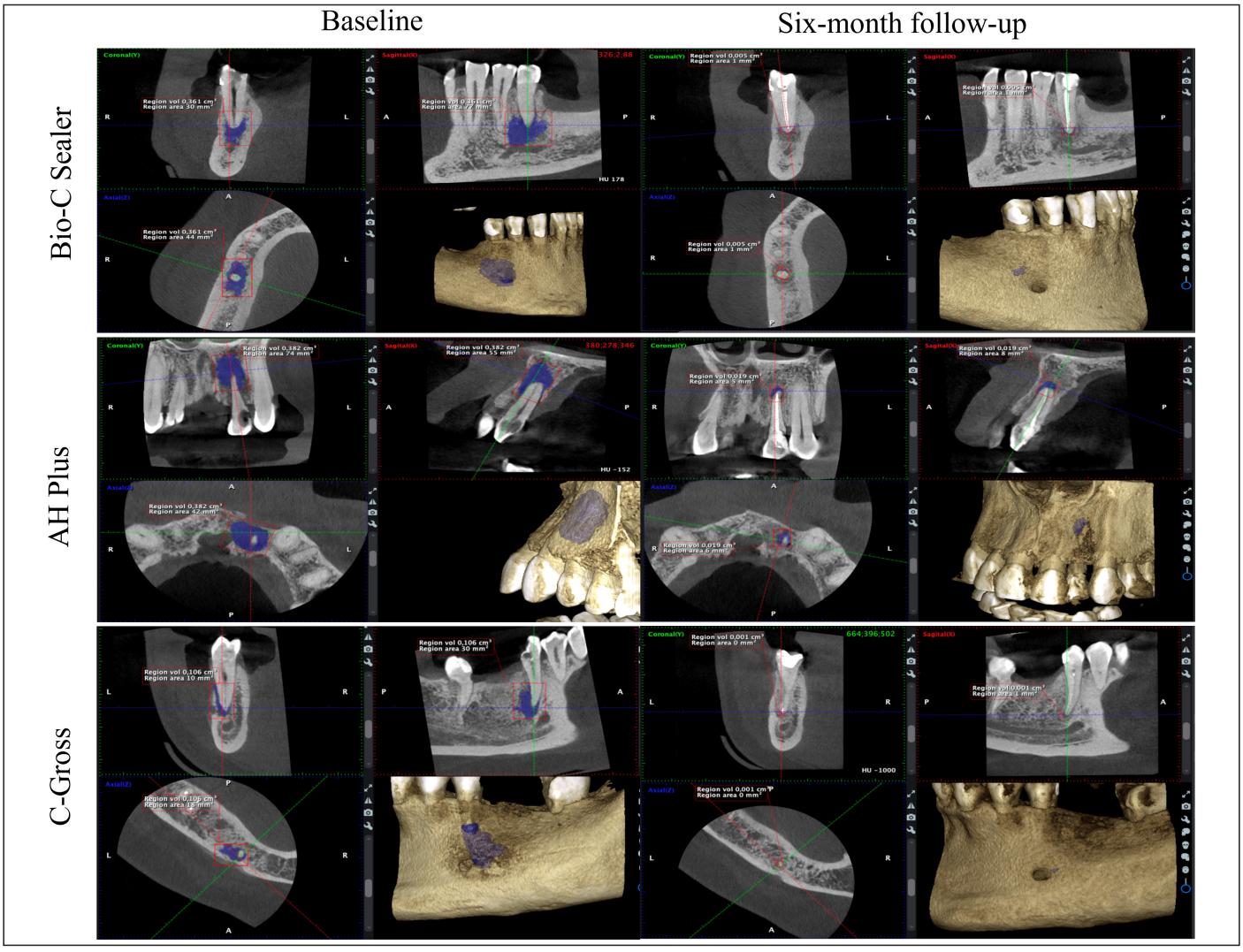


Figure 2. Multiplanar CBCT reconstructions and 3-dimensional renderings showing preoperative (left) and 6-month follow-up (right) periapical lesion segmentations across representative cases from the 3 sealer groups. Axial, sagittal, and coronal views illustrate manual boundary tracing and automated volumetric computation (blue contours), with corresponding 3D surface models depicting lesion morphology and spatial changes over time.

additional 3-dimensional insight at the individual tooth level without affecting the main comparative findings among sealers.

DISCUSSION

This prospective clinical trial using 3D-CBCT demonstrated that PA healing after single-visit endodontic treatment was not influenced by sealer type. All 3 sealers produced significant reductions in lesion volume at 6 months, with no differences among groups ($P < .05$). When canal disinfection, 3-dimensional obturation, and coronal sealing are optimally performed, PA repair occurs independently of sealer composition or leachate interactions. These results also show that single-visit therapy is highly predictable, regardless of preoperative PA lesions. The protocol was rigorously standardised to minimise confounders, isolating the sealer as the primary variable.

The CBCT imaging provides a 3-dimensional assessment of PA lesions, overcoming the limitations of 2-dimensional radiography and allowing more accurate volumetric evaluation of lesion size and healing progression.[14,17] Early bone repair and subtle changes in lesion volume, which are often undetectable on standard PA radiographs, can thus be reliably monitored.[18] In this study, CBCT was deemed necessary because the primary outcome was lesion volume reduction, requiring high-resolution 3-dimensional data, and because the clinical information could not be adequately obtained using lower-dose imaging. Following the 2025 AAE/AAOMR Joint Position Statement on the Use of CBCT in Endodontics, CBCT should be reserved for situations where the clinical information cannot be adequately obtained with lower-dose imaging, and the anticipated benefits outweigh the risks of radiation exposure. The statement emphasises adherence to the ALARA principle (As Low as Reasonably Achievable), the use of limited fields of view, and justification of each scan based on clinical necessity.[19] In this study, these recommendations were strictly followed: CBCT scans were limited to a small field of view, acquired pre-operatively and at 6 months, and restricted to bone-contained lesions. This ensured that CBCT use was both clinically indicated and ethically justified, providing high-resolution 3-dimensional data essential for accurate volumetric assessment of PA healing, while minimising patient radiation exposure.

All CETs were performed by postgraduate students under specialist supervision following a standardised protocol. Although this may introduce variability in manual execution, it situates the study within

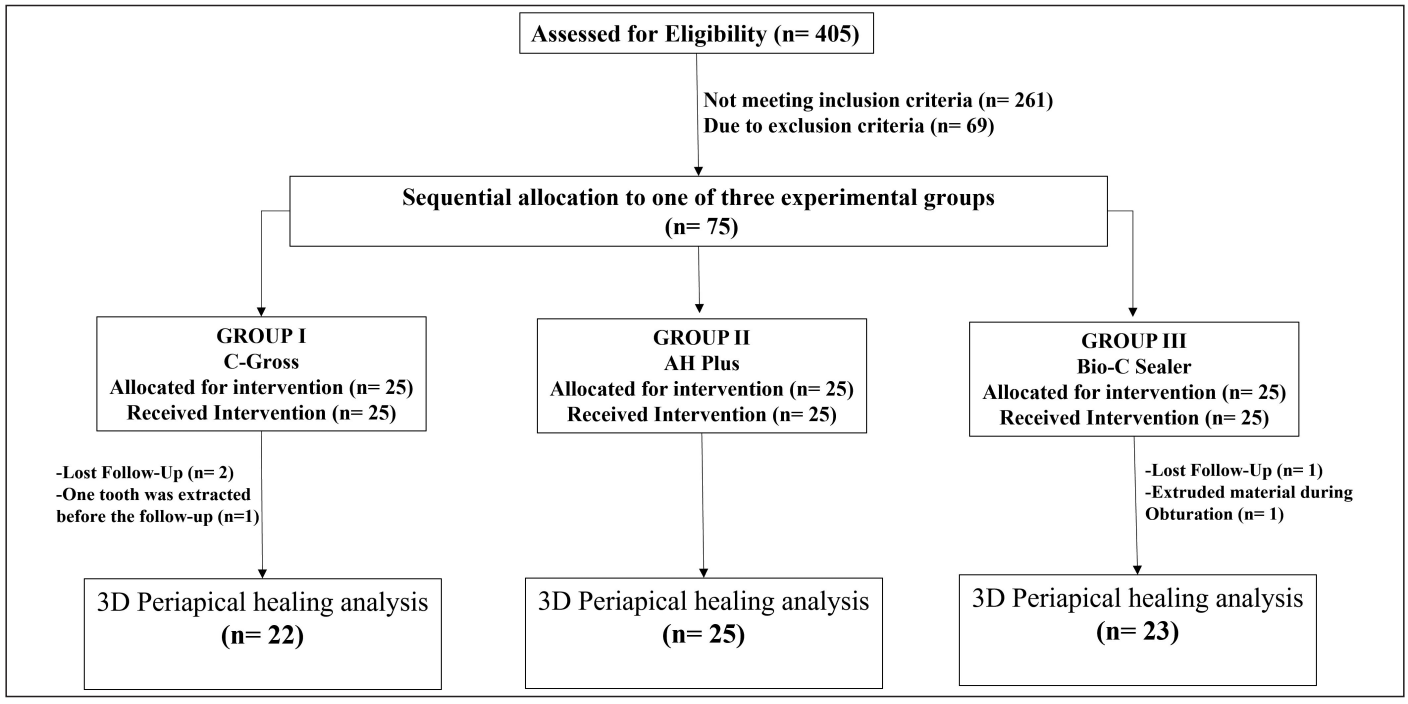


Figure 3. CONSORT flowchart illustrating the study design, including treatment protocols, patient attrition, and periapical healing assessment.

Table 1. Baseline Characteristics of the Treatment Groups

Characteristic		Treatment Groups				
		AH Plus	Bio-C Sealer	C-Gross	Test	*P*
Age, in years (mean)		48	49.3	44.18	2.1 (Kruskal–Wallis)	.35
Gender	Male	14 (56%)	9 (39.1%)	6 (27.3%)	4.05 (Chi-square)	.132
	Female	11 (44%)	14 (60.9%)	16 (72.7%)		

Age is presented as mean values, and gender as n (%). The groups did not differ significantly in age ($P = .35$) or gender distribution ($P = .132$), demonstrating balanced demographic characteristics across groups.

Table 2. Baseline (PRE) and 6-month (POST) Lesion Volumes for Each Sealer Group, Expressed as Mean (SD) and Median (Q1-Q3)

SEALER	n	PRE-mean mm³ (DE)	PRE-median mm³ (Q1-Q3)	POST-mean mm³ (DE)	POST-median mm³ (Q1-Q3)	Wilcoxon
AH Plus	25	109.60 (116.91)	81.00 [46.00-125.00]	26.08 (30.64)	15.00 [2.00-37.00]	$P < .001$
Bio-C sealer	23	83.87 (84.99)	63.00 [38.00-89.00]	19.74 (30.53)	12.00 [1.50-26.00]	$P < .001$
C-Gross	22	44.41 (40.29)	36.00 [11.75-61.25]	8.23 (10.91)	4.50 [1.00-10.50]	$P < .001$

All sealers demonstrated a significant intragroup reduction in volume over the 6 months (Wilcoxon, $P < .001$).

the framework of Real-World Data (RWD), as defined by the FDA and EMA,[20,21] reflecting clinical information obtained under routine conditions, including variability in operator skill, patient presentation, and biological response.[22] Conducted in a clinical setting with validated protocols and clinically relevant outcomes, this trial qualifies as RWD capable of generating Real-World Evidence (RWE), enhancing external validity and clinical applicability. Unlike single-operator studies portraying idealised scenarios, multi-operator RWD designs provide insight into how biologically based endodontic principles perform across diverse clinical contexts.[20-22]

Table 3. Percentage Reduction in Lesion Volume for Each Sealer Group, Expressed as Mean (SD) and Median (Q1-Q3)

Sealer	n	Mean (DE)	Median (Q1-Q3)
AH Plus	25	75.59 (24.39)	79.65 [63.41-95.03]
Bio C sealer	23	77.83 (21.60)	84.40 [65.91-98.27]
C-Gross	22	78.45 (22.00)	84.91 [69.84-93.13]

No significant differences were observed between sealers (Kruskal–Wallis, $P = .912$)

Periapical healing is a fundamental outcome of root canal therapy, reflecting inflammatory resolution, microbial elimination, and subsequent tissue repair. It is chiefly driven by the removal of antigenic and microbial stimuli from the root canal system, which reinstates the balance between osteoclastic resorption and osteoblastic regeneration

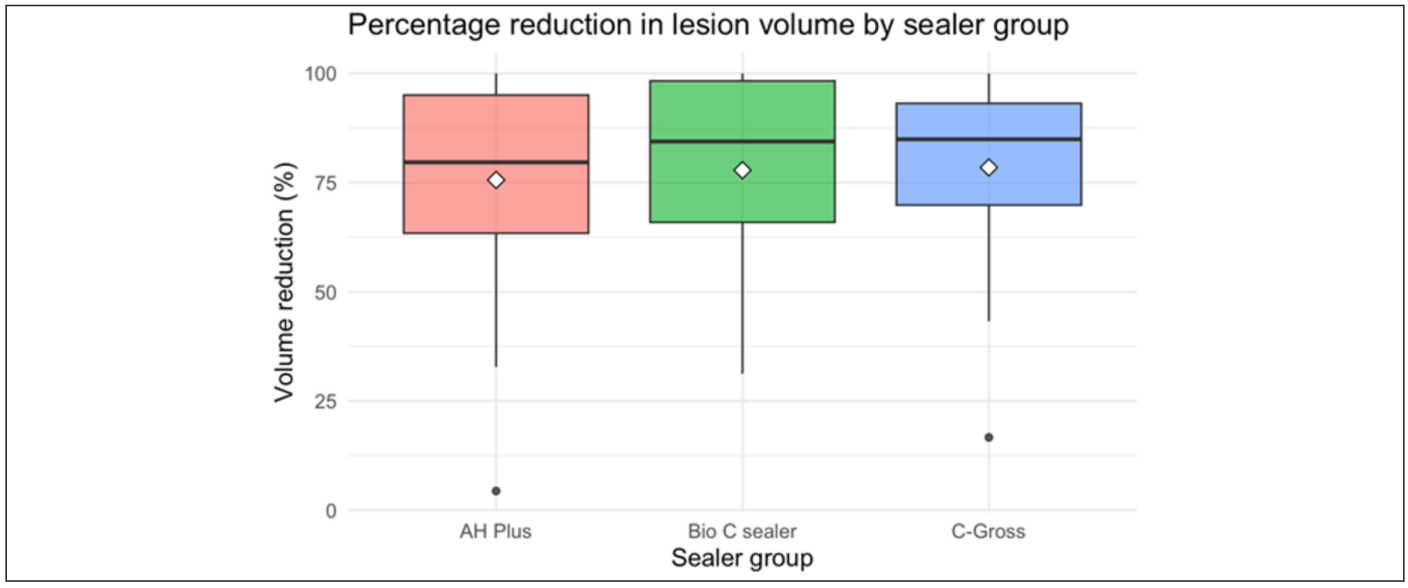


Figure 4. Percentage reduction in lesion volume across the 3 sealer groups. Boxplots show the distribution of volume reduction (%) for AH Plus, Bio-C Sealer, and zinc oxide–eugenol. The white diamond represents the mean value for each group. No significant differences were observed between sealers (Kruskal–Wallis, $P = .912$).

in the PA bone.[23] Once the inflammatory trigger is neutralised, the host's regenerative response predominates, promoting bone formation, periodontal ligament reorganisation, and progressive bio-mineralisation of the PA region.[5,23] At the molecular level, healing involves down-regulation of pro-inflammatory cytokines such as IL-1β, TNF-α,[3,4,24] inhibition of RANKL-mediated osteoclastogenesis, and activation of osteogenic pathways regulated by Runx2.[3,25] Beyond local factors, systemic conditions may influence PA repair following CET.[26] To minimise systemic confounding, the study included only ASA I-II patients and controlled smokers, ensuring that healing outcomes primarily reflected local biological processes rather than systemic disease effects.

The similar volumetric healing seen across the 3 sealers in this study can be partly explained by their shared ability to establish an effective apical seal, restrict the entry of irritants, and support a stable microenvironment that facilitates the host-driven biological repair process.

Table 4. Pairwise Post-hoc Comparisons for Absolute Volumetric Change (ΔVol) Among the 3 Sealer Groups

Post-hoc Comparisons for Absolute Volumetric Change (Δvol)		Post-hoc Comparisons for Percentage Reduction in PA Lesion Volume	
Comparison	Adjusted *P*	Comparison	Adjusted *P*
AH Plus - Bio-C sealer	1.000	AH Plus - Bio-C sealer	1
AH Plus - zinc oxide	.103	AH Plus - zinc oxide	1
Bio-C sealer - zinc oxide	.414	Bio C sealer - zinc oxide	1

The Kruskal–Wallis test showed no significant overall difference ($\chi^2 = 4.68$; $df = 2$; $P = .0963$). Dunn's post hoc test with Bonferroni correction revealed no significant pairwise differences between groups. Pairwise post-hoc comparisons for the percentage reduction in lesion volume among the 3 sealer groups. The Kruskal–Wallis test indicated no significant overall difference ($\chi^2 = 0.18$; $df = 2$; $P = .912$). Dunn's post-hoc test with Bonferroni correction showed no significant pairwise differences between groups.

The ZOE-based sealers (C-Gross) possess established antimicrobial activity due to eugenol release, which inhibits a broad range of endodontic microorganisms.[27,28] They also demonstrate acceptable dimensional stability and long-standing clinical performance.[29] Although eugenol elution can be dose-dependent and cytotoxic in vitro,[27-29] this effect diminishes substantially as the material sets and release decreases.[28] Importantly, in vivo evidence shows that ZOE does not hinder PA repair, with initial inflammation subsiding and normal healing progressing thereafter.[30]

The ERBS (AH Plus) provides strong adhesion to dentine and exhibits low solubility, contributing to a durable seal.[31,32] Its minimal polymerisation shrinkage supports long-term interfacial stability and reduces microleakage risk.[33] Biocompatibility studies report an initial, self-limiting inflammatory response, indicating acceptable tissue tolerance,[34] while fully set eluates show minimal cytotoxicity in vitro.[35] Overall, these properties suggest that PA healing with AH Plus is driven predominantly by host biological processes rather than sealer chemistry.

The CSCs (Bio-C Sealer) exhibit high biocompatibility, intrinsic bioactivity, and a hydraulic setting reaction that enables effective sealing in moist conditions.[36] Their release of Ca^{2+} and Si^{4+} ions may enhance bio-mineralisation and theoretically support PA repair.[37] However, this biological potential did not yield superior healing within the study timeframe. Despite their biocompatibility, alkalinity, and apatite-forming capacity, Bio-C produced volumetric outcomes comparable to C-Gross and AH Plus.

The outcomes of this trial align closely with the conclusions of recent systematic reviews and clinical studies, which have consistently reported no statistically significant differences in PA healing between ZOE-based sealers, ERBS and CSCs.[18,29,38-40] Khandelwal et al[8] reported in a systematic review that PA lesions showed significant healing after endodontic treatment regardless of sealer, although

Table 5. Descriptive Analysis of Apical Lesion Volume (mm^3) Before (PRE) and After (POST) Endodontic Treatment According to Sealer Type and Tooth Category

SEALER	Tooth Type	n	PRE-mean mm^3 (DE)	PRE-median mm^3 (Q1-Q3)	POST-mean (DE)	POST-median mm^3 (Q1-Q3)	Percentage Reduction
AH Plus	Anteriors	17	134.06 (132.56)	86.00 (73.00-148.00)	28.59 (31.55)	15.00 (3.00-46.00)	78.77
	Premolars	7	63.86 (46.34)	63.00 (36.00-82.50)	23.71 (31.03)	17.00 (1.00-29.50)	64.39
	Molars	1	14.00 (NA)	14.00 (14.00-14.00)	0.00 (NA)	0.00 (0.00-0.00)	100.00
Bio-C Sealer	Anteriors	11	66.36 (57.64)	65.00 (27.00-82.50)	29.73 (40.33)	21.00 (7.00-30.50)	67.97
	Premolars	12	99.92 (104.11)	62.50 (48.75-95.00)	10.58 (13.95)	4.50 (1.00-15.50)	86.86
C-Gross	Anteriors	16	43.88 (42.59)	28.50 (13.25-64.75)	9.81 (12.31)	5.00 (1.00-13.00)	77.79
	Premolars	6	45.83 (37.04)	46.50 (17.00-58.75)	4.00 (3.90)	3.50 (1.50-4.75)	80.23

Data are presented as mean (standard deviation, SD) and median with interquartile range (Q1-Q3). The percentage reduction represents the relative decrease in lesion volume from PRE to POST within each subgroup. *n* indicates the number of teeth analysed per sealer and tooth category.

bio-ceramic sealers appeared to have a slight advantage.[8] Bardini et al,[38] in a randomised controlled pilot study, observed a higher PA healing rate with bio-ceramic sealers compared to ZOE-based sealers following primary or secondary non-surgical treatment; however, the difference was not statistically significant, and both groups exhibited a progressive decrease in the PAI score.[38] In a 4-year follow-up randomised clinical trial, Bardini et al,[30] reported comparable success rates between CSC sealers applied with the single-cone technique and ZOE sealers with warm vertical compaction.[30] Similarly, Wahbi et al,[39]demonstrated that successful outcomes were achieved in untreated or retreatment cases of maxillary incisors with large PA lesions using either a bio-ceramic sealer with single-cone obturation or AH Plus with cold lateral condensation, with no significant differences between groups.[38] Furthermore, Pandey et al,[40] reported no discernible differences in PA healing at 6 months between ZOE-based, ERBS, and CSC-based sealers in a randomised controlled trial.[40] A possible explanation for minor discrepancies among previous trials lies in the imaging method used: most clinical studies relied on 2-dimensional radiographs, which underestimate lesion volume and overestimate healing.[8,41]

These findings highlight a critical need to re-evaluate the concept of bioactivity in endodontic materials. While calcium silicate–based sealers are often promoted for their capacity to induce hydroxyapatite formation,[36,37] the results, together with current clinical evidence,[8,30,38-40] demonstrate that such chemical reactivity does not automatically confer superior PA healing compared with traditional sealers (ZOE-based or epoxy-resin-based). This disconnect between in vitro bioactivity and in vivo clinical outcomes underscores the risk of overinterpreting physicochemical properties as predictive of biological performance. Consequently, bioactivity should be regarded strictly as a material characteristic, not as a surrogate for clinical efficacy. Future research must rigorously interrogate the relationship between sealer chemistry, host tissue response, and verified volumetric healing, bridging the gap between laboratory observations and true clinical outcomes.

While the present study focused on volumetric PA healing, material selection may influence other patient-centred outcomes, particularly postoperative pain. Bugea et al[42] (2022) evaluated postoperative discomfort in teeth with baseline PAI scores of 1 (absence of periapical lesions), and thus did not assess healing of apical pathology. However, their findings demonstrated that bioceramic sealers were associated with significantly reduced postoperative pain and lower analgesic consumption compared to ZOE-based sealers ($P < .05$). Although sealer composition does not appear to influence PA repair—as evidenced by comparable volumetric outcomes in the present study—it may affect immediate postoperative comfort, representing a relevant consideration in material selection beyond radiographic healing outcomes.

Limitations

Despite the strengths of this prospective, multi-operator study employing standardised protocols and 3D-CBCT volumetric analysis, several limitations should be acknowledged. First, patients were consecutively recruited using a non-probabilistic design with sequential allocation to the 3 experimental groups. This approach ensured inclusion of all eligible cases within the study period and reflects the clinical heterogeneity characteristic of real-world practice, thereby enhancing external validity compared with tightly controlled randomised designs. However, the lack of randomisation introduces potential baseline imbalance and selection bias. These risks were minimised through strict inclusion criteria and a fully standardised treatment protocol, reducing operator- and procedure-related variability while retaining the study's pragmatic character. Second, the follow-up duration was limited to 6 months, allowing evaluation of early lesion volume reduction as a positive indicator of healing dynamics; however, this time frame is insufficient to assess complete PA healing or long-term treatment success, particularly in teeth with chronic AP. The study appropriately reports lesion reduction, but not definitive lesion resolution. Longer follow-up (e.g., ≥24 months), ideally using a stepwise radiographic protocol with PA radiographs at intermediate intervals and CBCT only if clinically indicated at later stages, would provide a more comprehensive assessment while adhering to the ALARA principle. Finally, the study was conducted in single-rooted teeth with asymptomatic AP, limiting generalisability to multi-rooted teeth, retreatments, or cases with complex anatomical variations.

Future Perspectives

Future research should address the above limitations and further clarify the clinical relevance of sealer properties in endodontic healing. Randomised controlled trials with extended follow-up periods (>12 months) are warranted to evaluate long-term volumetric changes and potential differences among sealers over time. Multicentre studies including diverse tooth types, retreatment cases, and varying lesion sizes and anatomies could enhance external validity.

Moreover, combining clinical outcomes with molecular or histological biomarkers could provide a more comprehensive understanding of host–material interactions, helping to distinguish true biological effects from purely physicochemical phenomena. Finally, the relationship between sealer bioactivity, ion release, and actual PA tissue repair remains to be elucidated, supporting the need for translational studies bridging in vitro observations with clinically verified biological outcomes.

CONCLUSION

No significant volumetric differences were detected among calcium-silicate, epoxy resin, and ZOE sealers, indicating that once canals are disinfected and obturated 3-dimensionally, sealer composition has minimal impact on tissue repair. PA healing is predominantly host-driven, determined by inflammatory resolution and bone remodelling rather than by sealer-derived ion release or bioactivity. Although bioceramic sealers offer technical advantages, there is no evidence to support their superiority in biological healing. Comparable outcomes with ZOE and AH Plus further reinforce this principle. While in vitro studies demonstrate ion exchange and leachate activity, these appear clinically irrelevant when disinfection, obturation, and coronal sealing are properly achieved.

Disclosures

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the University Colegios de colombia (UNICOC) (Approval no: 19-10-2022-5, Acta 40; Date: October 19, 2022).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

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