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ORIGINAL ARTICLE

A 4-year follow-up of root canal obturation using a calcium silicate-based sealer and a zinc oxide-eugenol sealer: A randomized clinical trial

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Abstract

Aim: This randomized clinical trial assessed the outcomes of nonsurgical root canal treatment (RCT), comparing a calcium silicate-based sealer (CSBS) with the single-cone technique (SC) with a zinc oxide-eugenol (ZOE) sealer and warm vertical compaction (WVC).

Methodology: Ninety-two single- and multi-rooted teeth were divided into two groups and treated using either the SC with BioRoot™ RCS (BIO) or WVC with Pulp Canal Sealer™ EWT (PCS). Teeth with apical periodontitis (AP) in both groups were further divided into BIOAP and PCSAP subgroups. Standardized instrumentation and disinfection protocols were followed. Periapical index (PAI) was recorded, and clinical and radiographic follow-ups were conducted at 1, 3, 6, 12, 24, and 48 months. Outcomes considered included success rate (under strict and loose criteria), extraction, length of filling, voids, and extrusion rate, as well as changes in PAI score from baseline. Outcome variables and prognostic factors were analysed using binary and multiple logistic regression at $p < .05$.

Results: Sixty-seven teeth were included (recall rate, 73%). At 4-year follow-up, the overall success rates (BIO + PCS) were 89.6% by loose criteria and 83.3% by strict criteria. Subgroup success rates (BIOAP+PCSAP) were 88.5% by loose criteria and 80.4% by strict criteria. There were no significant differences between the groups in terms of success rate, extraction rate, length of filling, voids, or extrusion ($p > .05$). The pattern of PAI reduction was similar in both groups ($p = .806$).

Conclusion: Treatment using the SC-CSBS technique and the ZOE sealer with the WVC technique demonstrated a similar success rate.

KEYWORDS

bioactive sealers, calcium silicate-based sealers, endodontic outcome, root canal obturation, single cone technique

INTRODUCTION

Apical periodontitis (AP) is a chronic disease in which endodontic infection induces an inflammatory reaction within the periapical tissues, resulting in bone resorption and lesion formation (Márton & Kiss, 2014; Nair, 1997; Ricucci & Siqueira, 2010). A thorough root canal treatment (RCT) can prevent or treat AP (Ng et al., 2011a). According to the literature, the estimated weighted success rates of primary and secondary RCTs range between 68%–85% and 70%–86%, respectively. However, when loose criteria are applied, the success rates increase to 97% (Ng et al., 2011a, Ng, Mann, & Gulabivala, 2008, Ng, Mann, Rahbaran, et al., 2008, Ng et al., 2007). The quality of root canal filling is a significant prognostic factor influencing the success of nonsurgical RCTs (Ng, Mann, Rahbaran, et al., 2008). According to the European Society of Endodontology quality guidelines for endodontic treatments (Löst, 2006), approximately 40%–60% of the failures are related to inadequate obturation of the root canal system. State-of-the-art endodontic obturation should seal the entire root canal system, preventing microorganisms and fluids from passing through the canal to the apical tissues (AAE, 2016; Buchanan, 2015; European Society of Endodontology, 1994).

Various filling techniques have been proposed over the years (de Chevigny et al., 2008; Farzaneh, Abitbol, Lawrence, & Friedman, 2004; Orstavik et al., 1986), and recently, a variety of calcium silicate-based sealers (CSBSs) have been introduced to the market (Camps et al., 2015; Gomes-Filho et al., 2012; Lee et al., 2014; Torabinejad et al., 2018; Zhang et al., 2010a; Zhou et al., 2015). CSBSs exhibit hydraulic properties, allowing them to set and seal in the presence of moisture (Camilleri et al., 2022). They also demonstrate bioactivity; when in contact with tissue fluids, CSBSs release calcium ions and produce calcium hydroxide and apatite on their surfaces, potentially creating an interfacial layer between the sealer and dentinal walls (Donnermeyer et al., 2019; Salles et al., 2012; Sfeir et al., 2021; Wang, 2015). Additionally, a decreased inflammatory response has been observed in the bone in the presence of these products (Assmann et al., 2015; Wang et al., 2014; Zhang et al., 2010b). One example of CSBSs is the BioRoot™ RCS (Septodont, Saint-Maur-de-Fossés, France), a powder/liquid tricalcium silicate-based sealer introduced in 2015. It is recommended for use with the single-cone (SC) or cold lateral compaction root filling.

In the last decade, these innovative sealers have been extensively evaluated by comparing their properties to those of zinc oxide-eugenol (ZOE)-based and epoxy resin-based sealers in numerous *in vitro* studies (Alves Silva et al., 2020; Bardini et al., 2022; Donnermeyer et al., 2018; Drukteinis et al., 2021; Gaudin et al., 2020; Seo et al., 2019). However, they have seldom been tested in clinical trials (Bardini et al., 2021; Chybowski et al., 2018; Hu et al., 2022; Kim et al., 2022; Pontoriero et al., 2023), and there is a paucity of information from randomized controlled prospective clinical trials at medium- or long-term follow-up (Kim et al., 2022).

A randomized clinical trial, part of a modular project, has reported the results at 1-year follow-up of teeth instrumented with a standardized protocol and obturated using either the SC technique with gutta-percha (GP) and BioRoot™ RCS or warm vertical compaction (WVC) of GP and Pulp Canal Sealer™ EWT (Kerr© Corporation, Orange, CA), showing that both groups had similar good clinical performance (Bardini et al., 2021). The current study represents the second and third part of the project, aiming to evaluate the clinical outcome of teeth obturated with the two techniques and sealers, at 2- and 4-year follow-up, with the null hypothesis stating that there is no difference in the medium and long-term success rate in teeth obturated with the SC technique and a CSBS, or with the WVC technique and a ZOE sealer.

MATERIALS AND METHODS

Study design

This study was designed as a prospective, single-centre, randomized controlled clinical trial to compare the quality of root canal obturation and its short-, medium-, and long-term clinical outcomes in the general patient population. The trial was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice after receiving approval from the Ethics Committee (PROT. PG/2017/16759, Ca, November 2017) and registered at ClinicalTrials.gov (Identifier: NCT04249206). This randomized clinical trial has been written according to Preferred Reporting Items for Randomized Trials in Endodontics (PRIRATE) 2020 guidelines (Nagendrababu et al., 2020) (Figure 1).

Sample size

As the primary outcome, a mean difference between groups of 0.50 units (standard deviation 1.0) using the change in periapical index (PAI) score and a statistical power of 0.8 with a significance level of 0.05 was set. According to Pandis (Pandis, 2012), a minimum sample size of 41 dependent teeth with 26 participants per group was required. To account for potential dropouts throughout the study, we planned to recruit 10% more participants, resulting in a target of 46 dependent teeth and 28 patients per group.

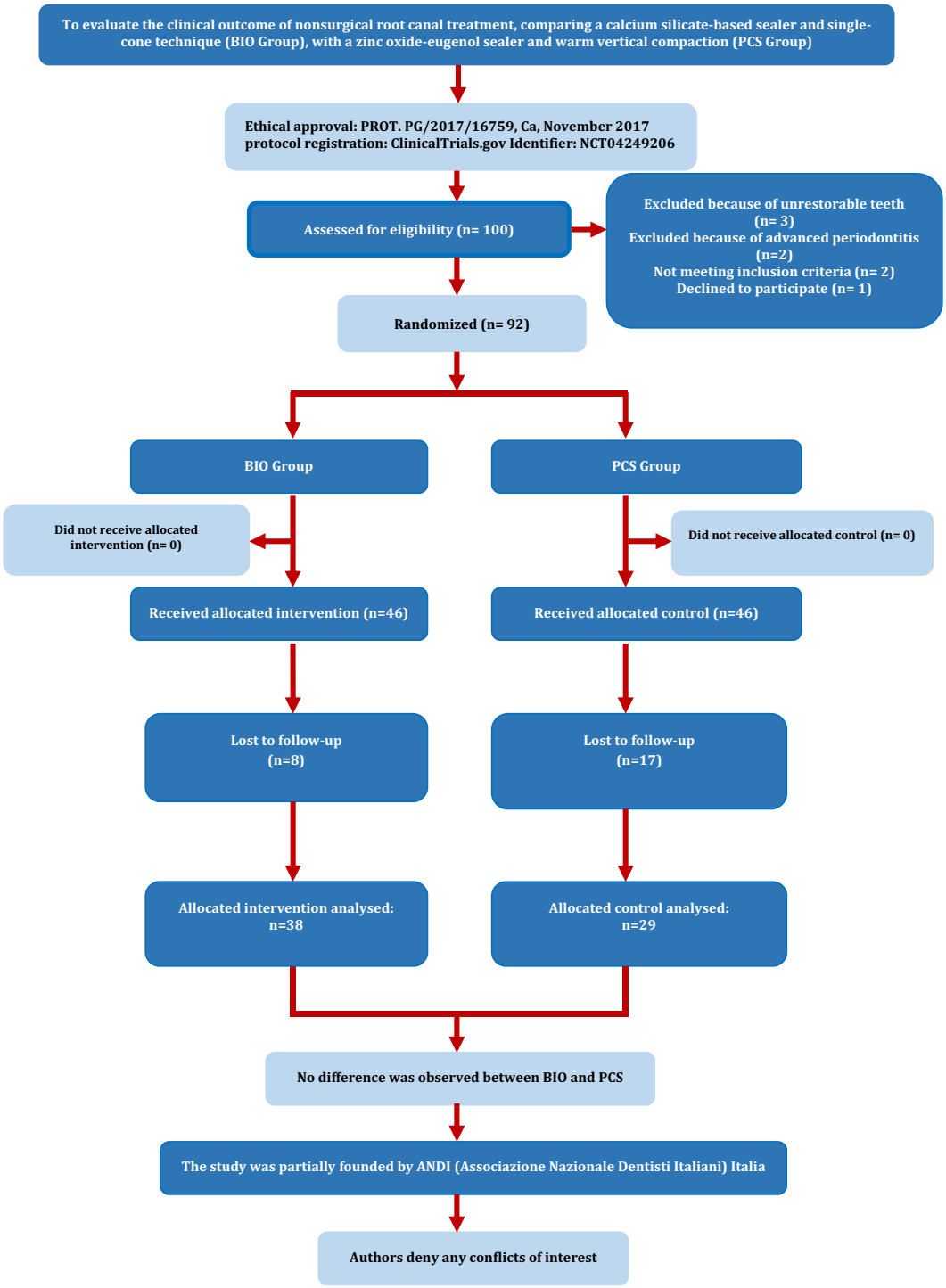

FIGURE 1 PRIRATE 2020 flowchart. From Nagendrababu, V et al. (2020). For further details, visit: http://pride-endodonticguidelines.org/prirate/.

Patient selection

Patients who met the following inclusion criteria were enrolled from the outpatient clinic of the Department of Conservative Dentistry and Endodontics at the University Hospital between 1 May 2016 and 31 December 2017: aged between 18 and 80 years, in good health (American Society of Anesthesiologists classification I or II) (De Cassai et al., 2019), and with at least one permanent single- or multi-rooted mature tooth with signs and/or symptoms indicating the need for endodontic treatment (primary or secondary) according to the ESE guidelines (Löst, 2006). The exclusion criteria were as follows: patients who did not agree to undergo RCT or participate in the study, had unrestorable teeth or teeth with poor prognosis (cracks, suspected fractures, iatrogenic perforations or resorptions, and moderate

to severe periodontitis), and had teeth requiring retreatment that displayed a poor prognosis due to a visibly altered root canal morphology (Gorni & Gagliani, 2004).

Inception cohort and randomisation

The following clinical and medical data were recorded before treatment: history of pain and responses to sensitivity tests, palpation, percussion, and periodontal probing (Berman & Hargreaves, 2015). At baseline, one or more periapical radiographs of Kodak ultraspeed dental film, size 31×41 mm (Carestream Health©, Stuttgart, Germany) and X-safe 70 70 KV/8 mA (Cefla Medical Equipment, Imola, Italy) of the involved teeth were obtained and evaluated to assess the crown, root, and periapical status. Written informed consent to undergo treatment, follow-up, and participate in the study was obtained from all patients prior to study enrolment.

A total of 56 patients with 92 single- or multi-rooted teeth fulfilled the inclusion criteria (Figure 1). All treatments were performed by four endodontic residents, divided into two groups depending on the day of the week on which they rotated in the clinics. The first patient on the list was randomly assigned by the clinical supervisor to either the SC with CSBS or the WVC with ZOE sealer, based on the outcome of flipping a coin. The second patient was assigned to the alternative technique, and the alternation continued until the end of the day. Random allocation ended when 46 teeth were assigned. Patients enrolled in the study were unaware of the treatment group to which they belonged.

Dental treatment

RCTs were performed using a standardized protocol that varied only in terms of the technique and sealer used for canal obturation.

Instrumentation and disinfection protocol

After local anaesthesia and rubber dam isolation, an access cavity was created, and the working length was assessed using an apex locator (DentalPort ZX, J. Morita MFG. CORP©, Kyoto, Japan), which was confirmed with one or more periapical radiographs. All the relevant radiographs (including preoperative, master apical file at working length, post-obturation, and follow-up periapical radiographs) were taken with consistent angulation ensured by the intuitive orientation of a beam-aiming device (Rinn; Dentsply Sirona, Ballaigues, Switzerland) (Ng et al., 2011b).

Primary RCTs were performed using NiTi ProTaper Next™ rotary instruments (Dentsply Sirona, Ballaigues, Switzerland) at 300 RMP and 4 N/cm in a crown-down approach. Each canal was prepared to at least an X2 master apical rotary file. In secondary RCTs, the GP and sealer were removed manually using Gates-Glidden drills and 0.1 mL of solvent (Endosolv® E, Septodont, Saint-Maur-des-Fossés, France). The canals were then manually renegotiated using K-files (Kerr© Corporation, Orange, California).

Throughout the instrumentation, root canals were continuously irrigated with 5.25% sodium hypochlorite (NaOCl) using a 31-gauge needle positioned 2 mm shorter than the working length (Niclor 5-Dentale, Ogna Lab, Muggiò, Italy). Once mechanical instrumentation was completed, each canal was irrigated with 5 mL of 5.25% NaOCl, followed by final irrigation with 5 mL of saline solution.

Root canal obturation methods

Following instrumentation, the canals were dried with sterile paper points. A standardized GP master cone, snugly fitting to the working length, was selected, and the canals were obturated as follows (Figures 1 and 2):

a. *BIO group*: BioRoot™ RCS was prepared according to the manufacturer's instructions. Obturation was completed by placing the GP master cone, previously coated with sealer, into the canal and removing excess GP with a heated instrument.
b. *PCS group*: Pulp Canal Sealer™ EWT was prepared according to the manufacturer's instructions, and obturation was performed according to the continuous wave technique (Buchanan, 1994). The GP master cone coated with the sealer was placed into the canal, and a pre-measured heated plugger (SuperEndo Alpha 2; B & L Biotech, Ansan, Korea) was inserted to cut and compact the master cone (Buchanan, 1994). Backfilling was performed through the thermoplastic injection of GP using SuperEndo Beta 2 (B & L Biotech).

A periapical radiograph was obtained to assess the quality of root canal filling. All teeth were restored coronally using composite resins and dental adhesives (IPS Empress Direct; Ivoclar Vivadent, Schaan, Liechtenstein, Germany). Any teeth requiring permanent full cuspal coverage were restored by the referring practitioner within 1 month of completing the RCT.

Follow-up assessment

Clinical examinations included assessing the presence or absence of pain, swelling, sinus tract, and abscess formation. Additionally, the functionality of each tooth was

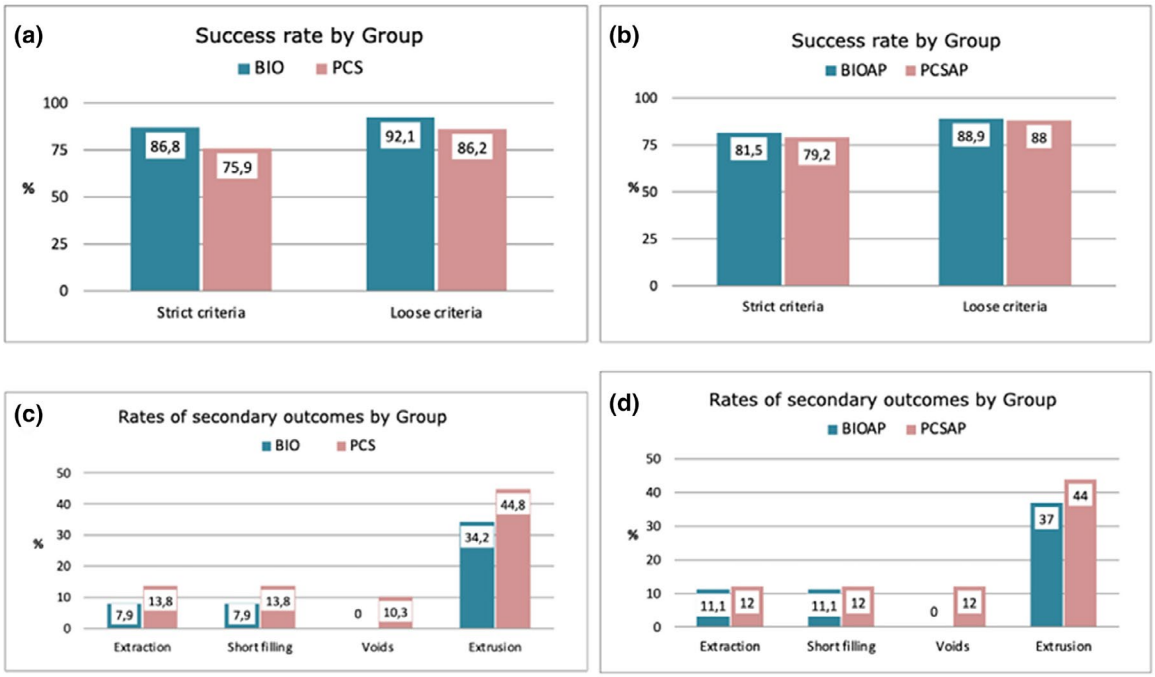

FIGURE 2 (a, b) Success rate by group. (c, d) Rates of secondary outcomes by group.

evaluated. Clinical and radiographic follow-ups were performed at 1, 3, 6, 12, 24, and 48 months for each tooth. Data were recorded in a dedicated chart and updated at every follow-up visit.

All radiographs were digitally scanned, saved in JPEG format, and imported into ImageJ software version 1.41 (National Institute of Health, Bethesda, MD, USA). Turbo Reg (Biomedical Imaging Group, Lausanne, Switzerland) was utilized to reduce the distortion factors in the radiographs (Bose et al., 2009). Preoperative and recall radiographs of the teeth were assigned PAI scores (Orstavik et al., 1986) by two blinded, trained, and calibrated examiners (Table S1) (Landis & Koch, 1977). Any disagreements were resolved by retaining the highest possible score. For multi-rooted teeth, the root with the highest score served as the reference. The same examiners assessed the quality of root canal obturation according to the criteria described by Ng et al. (2011a), Ng, Mann, Rahbaran, et al. (2008) (Table 1).

Quality of root canal obturation

The quality of the root canal obturation was evaluated based on criteria such as length, voids, and sealer extrusion (Table 1). Sealer extrusion and root-filling voids were classified as present or absent. For multi-rooted teeth, if sealer extrusion or root-filling voids were detected in at least one root, the teeth were categorized as having extrusions or voids. The root filling length was recorded as 'adequate', 'short', or 'long' (Siqueira et al., 2020; Sjögren et al., 1990).

Healing

After assigning a PAI score, each tooth was categorized based on clinical and radiographic assessments into the following outcome categories (Figure S1):

1. Healed: functional and asymptomatic without any sign of AP (PAI = 1).
2. Healing: functional and asymptomatic with periapical lesions that have decreased in size (PAI >1).
3. Diseased: non-functional and symptomatic teeth with signs of AP (PAI >1) or asymptomatic teeth with increased periapical lesions.

Functional teeth were defined as teeth without symptoms, whether with newly emerged or persisting, or without AP (Friedman & Mor, 2004).

According to the loose criteria, both healed and healing cases were classified as successful. Strict criteria considered only healed cases as successful (Tables 1 and 2) (Ng, Mann, & Gulabivala, 2008).

The entire tooth was assessed as a unit. If a tooth was extracted due to endodontic problems such as persistent pain, swelling, sinus tract, or periapical radiolucent lesions, the treatment outcome was considered a failure (Table 1).

TABLE 1 Descriptive table at tooth level by groups.

	Group											
	Total		BIO		PCS		Total		BIOAP		PCSAP	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Sex												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Male	27	40.3	11	28.9	16	55.2	20	38.5	7	25.9	13	52.0
Female	40	59.7	27	71.1	13	44.8	32	61.5	20	74.1	12	48.0
Age (years)												
N	67	–	38	–	29	–	52	–	27	–	25	–
Mean	54.2	–	53.4	–	55.3	–	53.9	–	53.9	–	53.8	–
Standard deviation	16.7	–	14.7	–	19.3	–	17.7	–	15.8	–	19.9	–
Median	49.0	–	49.0	–	50	–	49.0	–	49.0	–	46.0	–
Age group												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
<45 years	21	31.3	11	28.9	10	34.5	18	34.6	8	29.6	10	40.0
45–60 years	22	32.8	15	39.5	7	24.1	15	28.8	10	37.0	5	20.0
>60 years	24	35.8	12	31.6	12	41.4	19	36.5	9	33.3	10	40.0
Tooth type												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Incisor	19	28.4	13	34.2	6	20.7	19	36.5	13	48.1	6	24.0
Canine	6	9.0	3	7.9	3	10.3	4	7.7	2	7.4	2	8.0
Premolar	15	22.4	10	26.3	5	17.2	9	17.3	4	14.8	5	20.0
Molar	27	40.3	12	31.6	15	51.7	20	38.5	8	19.6	12	48.0
Arch												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Maxilla	31	46.3	17	44.7	14	48.3	26	50.0	13	48.1	13	52.0
Mandible	36	53.7	21	55.3	15	51.7	26	50.0	14	51.9	12	48.0
Rct type												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Primary	50	76.4	29	76.3	21	72.4	38	73.1	20	74.1	18	72.0
Secondary	17	25.4	9	23.7	8	27.6	14	26.9	7	25.9	7	28.0
Apical patency												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	7	10.4	3	7.9	4	13.8	6	11.5	3	11.1	3	12.0
Yes	60	89.6	35	92.1	25	86.2	46	88.5	24	88.9	22	88.0
Pulp diagnosis												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Vital	12	17.9	9	23.7	3	10.3	–	–	–	–	–	–
Necrotic	38	56.7	20	52.6	18	62.1	38	73.1	20	74.1	18	72.0
Pulpless	17	25.4	9	23.7	8	27.6	14	26.9	7	25.9	7	28.0
AP diagnosis												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Normal	12	17.9	9	23.7	3	10.3	–	–	–	–	–	–

TABLE 1 (Continued)

	Group											
	Total		BIO		PCS		Total		BIOAP		PCSAP	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Asymptomatic AP	15	22.4	9	23.7	6	20.7	12	23.1	7	25.9	5	20.0
Symptomatic AP	38	56.7	18	47.4	20	69.0	38	73.1	18	66.7	20	80.0
Chronic AP	2	3.0	2	5.3	0	.0	2	3.8	2	7.4	0	.0
Extracted teeth												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	60	89.6	35	92.1	25	86.2	46	88.5	24	88.9	22	88.0
YES	7	10.4	3	7.9	4	13.8	6	11.5	3	11.1	3	12.0
Extraction time												
Total	7	100.0	3	100.0	4	100.0	7	100.0	3	100.0	4	100.0
T3	1	14.3	1	33.3	0	.0	1	14.3	1	33.3	0	.0
T4	1	14.3	0	.0	1	25.0	1	14.3	0	.0	1	25.0
T5	5	71.4	2	66.7	3	75.0	5	71.4	2	66.7	3	75.0
Filling length												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
Short	7	10.4	3	7.9	4	13.8	6	11.5	3	11.1	3	12.0
Normal	60	89.6	35	92.1	25	86.2	46	88.5	24	88.9	22	88.0
Long	–	–	–	–	–	–	–	–	–	–	–	–
Voids												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	64	95.5	38	100.0	26	89.7	49	94.2	27	100.0	22	88.0
Yes	3	4.5	0	.0	3	10.3	3	5.8	0	.0	3	12.0
Sealer extrusion												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	41	61.2	25	65.8	16	55.2	31	59.6	17	63.0	14	56.0
Yes	26	38.8	13	34.2	13	44.8	21	40.4	10	37.0	11	44.0
Success, strict criteria (2 years)												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	15	22.4	7	18.5	8	27.6	14	26.9	7	25.9	7	18.0
Yes	52	*77.6*	31	81.5	21	72.4	38	*73.1*	20	74.1	18	72.0
Success, loose criteria (2 years)												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	7	10.4	3	7.9	4	13.8	6	11.5	3	11.1	3	12.0
Yes	60	*89.6*	35	92.1	25	86.2	46	*88.5*	24	88.9	22	88.0
Success, strict criteria (4 years)												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	11	16.7	5	13.2	6	21.4	10	19.6	5	18.5	5	20.8
Yes	56	*83.3*	33	86.8	23	78.6	42	*80.4*	22	81.5	20	79.2
Success, loose criteria (4-years)												
Total	67	100.0	38	100.0	29	100.0	52	100.0	27	100.0	25	100.0
No	7	10.4	3	7.9	4	13.8	6	11.5	3	11.1	3	12.0
Yes	60	*89.6*	35	92.1	25	86.2	46	*88.5*	24	88.9	22	88.0

TABLE 2 Results of multiple binary logistic regression (adjusted OR and 95% CI, *p*-value) with GEE model estimation.

Outcomes	Group and other factors	OR	95% CI	*p*-value
Strict criteria	*BIO*	1		
	PCS	0.40	0.11–1.47	.166
	Sex			
	Male	1	0.14–2.03	.351
	Female	0.53		
	Age	1.04	1.00–1.07	**.035***
	BIOAP	1		
	PCSAP	0.90	0.23–3.57	.885
	Age	1.04	1.00–1.07	**.047***
Loose criteria	*BIO*[a]	1		
	PCS[a]	0.41	0.10–1.63	.207
	Sex			
	Male	1		
	Female	0.24	0.02–2.34	.216
	RCT type			
	Primary	1		
	Secondary	0.30	0.09–1.07	.064
	BIOAP	1		
	PCSAP	0.87	0.18–4.29	.871
	AP Diagnosis			
	Normal	–	–	–
	Asymptomatic AP	1		
	Symptomatic AP	3.95	0.85–18.3	.079
	Chronic AP	–	–	–
Extractions rate	*BIO*[a]	1		
	PCS[a]	2.43	0.61–9.68	.207
	Sex			
	Male	1		
	Female	4.26	0.43–42.3	.216
	RCT type			
	Primary	1		
	Secondary	3.32	0.93–11.8	.064
	BIOAP	1		
	PCSAP	1.15	0.23–5.65	.865
	AP Diagnosis			
	Normal	–	–	–
	Asymptomatic AP	1		
	Symptomatic AP	0.25	0.06–1.17	.079
	Chronic	–	–	–
Short filling rate	*BIO*	1		
	PCS	1.89	0.42–8.60	.409
	Sex			
	Male	1		
	Female	1.06	0.24–4.58	.943

TABLE 2 (Continued)

Outcomes	Group and other factors	OR	95% CI	*p*-value
	BIOAP	1		
	PCSAP	1.09	0.18–6.57	.924
	Sex			
	Male	1		
	Female	1.29	0.20–8.78	.793
Extrusion rate	*BIO*	1		
	PCS	1.30	0.41–4.15	.656
	Sex			
	Male	1		
	Female	0.47	0.14–1.60	.226
	Arch			
	Maxilla	1		
	Mandible	0.32	0.12–0.91	**.032***
	BIOAP	1		
	PCSAP	1.31	0.41–4.11	.649
	Arch			
	Maxilla	1		
	Mandible	0.32	0.10–1.02	.054

Note: Success rate under strict and loose criteria by Group and other factors, extraction, short filling, and extrusion rate by group and other factors.

*$p < .05$.

[a]Pulp and AP diagnosis were excluded to achieve the convergence of the model.

Outcome variables

Healing was designated as the primary outcome of the study. Several secondary outcomes were evaluated, including extraction rates, length of filling, presence of voids, and sealer extrusion rate. For the subgroups BIOAP and PCSAP, the measurement of PAI score at different time points (T0: baseline, T1: 1 month, T2: 3 months, T3: 6 months, T4: 1 year, T5: 2 years, T6: 4 years), and changes in PAI values compared to baseline (T1-T0, T2-T0, T3-T0, T4-T0, T5-T0, and T6-T0) were considered as tertiary outcomes.

Statistical analysis

The statistical analysis included descriptive statistics for categorical variables (absolute and relative frequencies) and continuous variables (mean, standard deviation, range, median, and quartiles) for the total sample and by group differentiation. Binary outcomes were compared between groups using multi-level simple binary logistic regression with generalized estimation equations (GEE). Raw odds ratio (OR) and 95% confidence intervals were obtained from Wald's Chi^2 statistic. Quantitative outcomes were analysed by linear regression models and estimated with GEE to account for within-subject dependence of teeth. Beta coefficients and 95% confidence intervals were reported for these analyses.

The homogeneity of groups concerning patient profiles and clinical variables at baseline was assessed using linear and logistic models with GEE. The significance level was set at 5% ($p < .05$). STATA version 17 (STATA Corp., TX, US) was used for all statistical analyses.

RESULTS

Of the 100 teeth assessed for eligibility, 8 were excluded (Figure 1). The original study group consisted of 56 patients with 92 randomized treated teeth. However, 25 teeth were lost to follow-up at the 2- and 4-year appointments and were subsequently excluded from the analysis (Figures 1 and 2).

Accordingly, 45 patients were included in the outcome assessment, comprising 20 male (44.4%) and 25 female patients (55.6%), with an average age of 53.6 ± 16.6 years ranging from 28 to 84 years at baseline. On average, each patient contributed 1.5 teeth, resulting in a total sample of 67 teeth (73% recall rate) (Table 1 and Figure 1). The distribution of teeth was as follows:

BIO group: 38 teeth in 22 patients, obturated using the SC technique and BioRoot™ RCS;

PCS group: 29 teeth in 18 patients, obturated using the WVC of GP and Pulp Canal Sealer™ EWT.

Teeth with AP from both groups were further divided into two subsamples:

BIOAP: 27 teeth in 18 patients in the BIO group.

PCSAP: 25 teeth in 17 patients in the PCS group (Table 1 and Figure 1).

Analysis regarding group homogeneity revealed that BIOAP and PCSAP were homogeneous, whereas BIO and PCS were homogeneous in most variables, except for the distribution of teeth by sex. Teeth from female patients were more frequent in the BIO than in the PCS group ($p = .046$) (Table S2). Therefore, sex distribution was considered a potential confounder and was entered into adjusted models to control for its influence.

The kappa scores for inter-examiner and intra-examiner agreement were 0.86 and 0.91, respectively, indicating good agreement (Landis & Koch, 1977).

Two-year follow-up

Based on loose criteria, the overall success rate of both groups (BIO + PCS) and subgroups (BIOAP + PCSAP) was 88.46% and 89.55%, respectively (Table 1). Upon comparing BIO and PCS and BIOAP and PCSAP, similar success rates were obtained (Table 1).

When strict criteria were applied, the overall success rate in both groups (BIO + PCS) and subgroups (BIOAP + PCSAP) was 73.08% and 77.61%, respectively (Table 1). Upon comparing BIO and PCS and BIOAP and PCSAP, similar outcomes were observed (Table 1).

Four-year follow-up

Primary outcome

Based on loose criteria, the total success rates of groups (BIO + PCS) and subgroups (BIOAP + PCSAP) were 89.6% and 88.5%, respectively (Table 1). Comparison between BIO and PCS and BIOAP and PCSAP showed that both techniques performed similarly (OR = .54; $p = .336$ and OR = .92; $p = .904$, respectively) (Table 2 and Figure 2a,b).

Results of simple binary logistic regression for 'BIO and PCS and other factors' revealed that secondary treatments had the probability of success reduced to 79% (OR = .21; $p = .023$), pulpless teeth had the odds of success reduced with respect to necrotic teeth (OR = .28; $p = .064$), and symptomatic AP showed increased odds of success compared to asymptomatic AP (OR = 4.24; $p = .040$). In subgroups BIOAP and PCSAP, symptomatic AP had increased odds of success compared to asymptomatic AP (OR = 3.89; $p = .074$) (Table S3). Multiple binary logistic regression with GEE model estimation did not identify any difference by group ($p = .207$) or subgroup ($p = .871$) (Table 2).

When strict criteria were considered, the total success rate of groups and subgroups decreased to 83.3% and 80.4%, respectively (Table 1). Both techniques (BIO and PCS; BIOAP and PCSAP) showed similar results (OR = .48; $p = .224$ and OR = .86; $p = .827$, respectively) (Table 2 and Figure 2a,b). In a simple binary logistic regression model by both groups and subgroups, age was detected as a significant covariate (OR = 1.04; $p = .047$ and OR = 1.04; $p = .052$, respectively) (Table S2). Multiple binary logistic regression with GEE model estimation did not identify any difference by group and subgroup ($p = .166$ and $p = .885$, respectively) (Table 2).

Secondary outcomes (extraction rate, length of filling, extrusion and presence of voids rate)

Both techniques in the groups and subgroups had a similar extraction rate (OR = 1.87; $p = .336$ and OR = 1.09; $p = .904$, respectively) (Table 2, Table S3 and Figure 2c,d). A simple binary regression by 'BIO and PCS and other factors' revealed that secondary treatments exhibited an increased probability of extraction (OR = 4.82; $p = .023$), pulpless teeth showed an increased risk of extraction compared to necrotic teeth (OR = 3.59; $p = .064$), and symptomatic AP showed reduced risk of extraction compared to asymptomatic AP (OR = .24; $p = .040$). In BIOAP and PCSAP, symptomatic AP reduced the probability of extraction (OR = .26; $p = .074$) (Table S3). When a multiple model was estimated, no differences were found by groups ($p = .207$) and subgroups ($p = .865$) (Table 2).

Both sealers and techniques in groups and subgroups showed no difference in the length of filling, and no factors influenced the probability of having short fillings (Table S3 and Table 2). Only three teeth showed voids, all of which were in the PCS and PCSAP groups (Table 1). A conventional Fisher's exact test indicated a strong tendency ($p = .076$ and $p = .104$). Both sealers showed no differences in terms of *extrusion* (Table S3 and Table 2). Mandibular teeth showed a lower probability of sealer extrusion (OR = .32; $p = .032$ and OR = .32; $p = .054$, respectively) (Table 2).

Tertiary outcomes

All teeth (100%) in both subgroups experienced a reduction of PAI from baseline to 4-year recall (Table S1). When a multiple model was estimated, no differences

were found by subgroup ($p = .684$) and PAI reduction was correlated with age ($p = .008$), as each additional year negatively influenced this reduction (−0.02) (Table 3). A non-parametric Brunner-Langer model for longitudinal data was conducted to study changes in PAI over time. An analysis of variance type-test statistics was used to estimate the main effects involving time. PAI dropped significantly over time ($p < .001$), but the pattern of reduction was similar in both groups ($p = .806$). Additionally, no overall differences in PAI were found among groups ($p = .786$), and this result extends to every time point ($p = .806$) (Table 4).

TABLE 3 Overall PAI reduction (T6-T0) by Group and other factors.

Group and other factors	Beta	95% CI	*p*-value
Group			
BIO	0		
PCS	−0.17	−0.77–0.44	.594
Sex			
Male	0		
Female	0.33	−0.34–0.99	.336
Tooth type			
Anterior	0		
Premolar	0.22	−0.60–1.05	.596
Molar	0.44	−0.19–1.06	.173
Pulp diagnosis			**.001****
Vital	0		
Necrotic	−2.68	−3.33– −2.02	**<.001*****
Pulpless	−1.88	−2.61– −1.14	**<.001*****
Group			
BIOAP	0		
PCSAP	0.12	−0.47–0.71	.684
Age	0.02	0.00–0.03	**.007****

Note: Results of multiple linear regression (adjusted Beta and 95% CI, *p*-value) with GEE model estimation.

**$p < 0.01$. ***$p < 0.001$.

TABLE 4 Changes at PI over time by Group: Results of ATS test from the Brunner-Langer model.

Group		*p*-value
BIO-PCS	TIME	**<.001*****
	GROUP	.129
	TIME × GROUP	.534
BIOAP-PCSAP	TIME	**<.001*****
	GROUP	.786
	TIME × GROUP	.806

***$p < .001$.

DISCUSSION

This study presents the 2- and 4-year follow-up results of a modular project assessing the outcomes of primary and secondary RCTs. The treatments involved either the SC technique with a CSBS or WVC of GP with a ZOE sealer, which serves as a classic reference treatment (Castellucci, 2019). We designed this randomized, controlled clinical trial to obtain early insights into the SC-CSBS technique because there is limited clinical information on the use of new hydraulic sealers with SC obturation. Our study was based on a stringent protocol to minimize bias, which could have affected the results.

This study represents the medium- and long-term follow-up phase following the initial 1-year report (Bardini et al., 2021). The decision to conduct frequent recalls initially (at 1, 3, and 6 months) followed by longer-term assessments (1, 2, and 4 years) was aimed at providing comprehensive insights into the behaviour of treated teeth. It also sought to evaluate whether the newer sealer used with the single-cone technique could promote faster or more complete healing compared to the traditional standard (Wang, 2015) (Figure 3 and Table S3). This information is valuable in clinical settings, especially for teeth with extensive lesions that require prosthetic rehabilitation.

The outcomes at 2 and 4 years were favourable and comparable in both treatment groups (Table 1 and Figure 2a,b). According to loose criteria, the overall success rate in our study (Table 1) was higher than that reported in a well-designed systematic review on endodontic outcome (Ng et al., 2007). Meanwhile, when applying strict criteria, our success rate aligned closely with the pooled weighted success rate noted by the same authors (Table 1) (Ng, Mann, Rahbaran, et al., 2008, Ng et al., 2007).

Factors such as voids, root canal filling length, and sealer extrusion did not show significant associations with the outcome; however, as discussed above, the clinical protocol was strictly controlled (Ng et al., 2011b; Sjögren et al., 1990) (Table 2).

Comparing the present outcomes with those at the 12-month recall (Bardini et al., 2021), the success rates based on loose criteria showed a reduction across all groups (BIO, PCS, BIOAP, and PCSAP) at the 2- and 4-year follow-ups (Table 1). Notably, this decrease may have been influenced by the loss of two patients and their respective teeth during the study period. In contrast, when using strict criteria, the success rates were higher across all groups over time (Table 1). This observation is consistent with previous findings indicating that the percentage of successful cases tends to improve with longer follow-up durations (Ng et al., 2007).

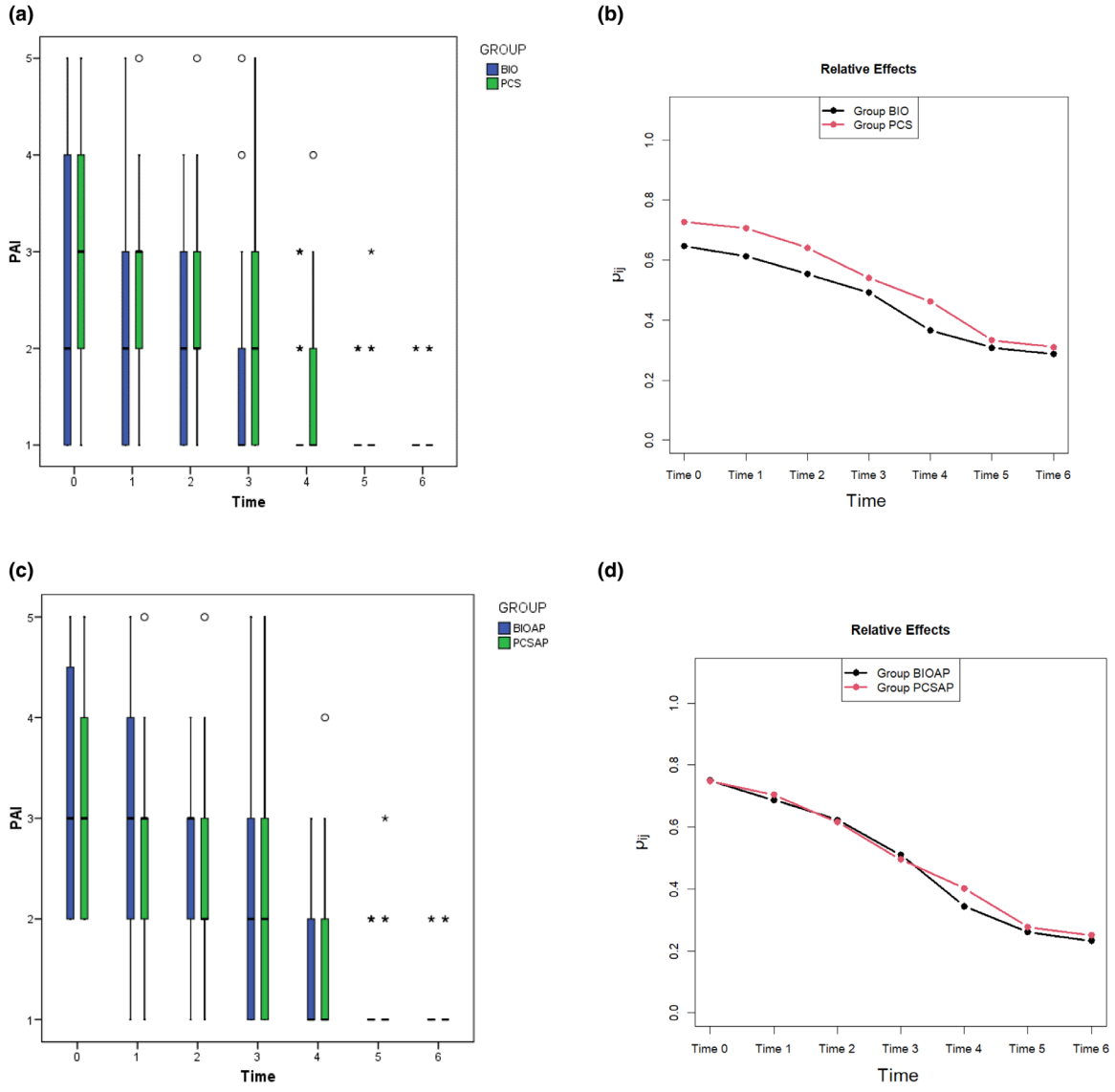

FIGURE 3 PAI score over time by group. (a, b) BIO and PCS. (c, d) BIOAP and PCSAP.

In this study, the combination of primary and secondary endodontic therapies was chosen to enhance the statistical analysis, a decision supported by literature suggesting that the periapical healing rates of secondary RCTs are only slightly lower than those of primary therapies (Farzaneh, Abitbol, & Friedman, 2004; Friedman et al., 2003; Ng et al., 2011a). This similarity becomes even more pronounced when the teeth requiring retreatment do not exhibit visibly altered root canal morphology (Gorni & Gagliani, 2004). However, our study results indicate that secondary treatment remains a marginally significant negative predictive factor for the outcome of root canal therapy (Table 2).

All the teeth in both subgroups with AP demonstrated a similar trend of healing, as supported by a significant reduction of PAI over time (Table S1 and Figure 3). Interestingly, this reduction was inversely correlated with age (Table 3), a common finding in previous studies (Ideo et al., 2024). However, the initial size of the lesion did not significantly influence this reduction (Ng et al., 2011b). These data seem promising, considering that larger lesions often present greater challenges for healing (Chybowski et al., 2018; Ng et al., 2011b), highlighting their potential as confounding variables in outcome evaluations (Gulabivala & Ng, 2023). Notably, preoperative symptomatic AP minimally affected the success and extraction rates in both subgroups (Table 2).

The results of the 2- and 4-year follow-up in this trial are consistent with those obtained from two previous clinical reports (Chybowski et al., 2018; Zavattini et al., 2020). Chybowski et al. (2018) retrospectively described a healing rate of 83.1% at an average of 30.1 months in 307 teeth treated by different specialists, while Zavattini et al. (2020) reported an overall success rate of 90% at

12 months for 53 treated teeth in a non-randomized case–control study conducted in a university setting. However, differences in the designs of these studies did not render the articles completely comparable. Both authors (Chybowski et al., 2018; Zavattini et al., 2020) considered healed and healing cases successful, whereas we defined two levels of outcome (Bardini et al., 2021; Ng et al., 2011a, 2011b). Additionally, two of the CBCSs tested in these three studies were the same (Bardini et al., 2021; Zavattini et al., 2020), whereas one was a different product (Endo Sequence Bioceramic Sealer, BC; Brasseler USA, Savannah, GA) (Chybowski et al., 2018). In a more recent randomized, case-control clinical trial, the efficacy of the SC technique and a third CSBS (Endoseal TCS Maruchi, Wonju, Korea) was compared with that of WVC and AH Plus (Dentsply International Inc., York, PA, USA). The recall rate was similar to the one in this study (79%) but with a lower average follow-up (17 months). The reported success rates for SC/CSBS and WVC/AH Plus were 94.3% and 92.3% (loose criteria) and 71.4% and 60.8% (strict criteria), respectively. Notably, a standardized instrumentation protocol was not established.

The most important limitation of this study is its small number of patients, leading to reduced statistical power and increased variability in dental conditions among participants. Another potential limitation of this study is the variability in operator skills, given that four postgraduate endodontic residents performed the RCTs. However, it is worth noting that a systematic review has indicated that both postgraduate students and specialists achieve high success rates in clinical studies, regardless of whether strict or loose criteria are applied (Ng et al., 2007).

Finally, in vitro reports have demonstrated that most of the available endodontic irrigants (NaOCl, CHX, and EDTA) may negatively affect the efficacy of CSBS (Arias-Moliz & Camilleri, 2016; Donnermeyer et al., 2018; Razmi et al., 2016). Therefore, the potential interactions between the final irrigation protocol and the management of CSBSs should be considered (Sfeir et al., 2021). However, the clinical implications of these interactions remain unclear. In our protocol, a final rinse was performed using sterile saline before the root canal was dried and obturated. Another important aspect related to this topic is the formulation of the CSBS. According to the manufacturers, moisture from the dentinal tubules tends to initiate the setting of premixed formulations (Silva Almeida et al., 2017). This trial used a powder/liquid tricalcium silicate-based sealer. This is a water-based sealer in which the switch from cement to sealer depends on the inclusion of a water-soluble polymer that allows the material to flow.

Another aspect currently under debate is the placement of sealers in the canal. SC obturation has been reported to induce a higher void ratio compared to WVC techniques, especially in oval or wide root canals (Mancino et al., 2021). When this study was designed, the available information regarding sealer placement techniques was obtained from the manufacturers. This explains why in this clinical trial neither sonic/ultrasonic activation nor sealer activation/agitation, and flexible injection tips have been used to improve CSBS distribution in the root canal space (Kim et al., 2018). Nonetheless, our results showed high success rates for both the BIO and BIOAP. As stated by other authors, the evidence regarding these clinical protocols remains weak (Sfeir et al., 2021).

Although further research is needed to confirm additional benefits of using bio-inductive materials in promoting periapical healing (Gulabivala & Ng, 2023), our study suggests that the sealer-based obturation technique performed with BioRootTM RCS and SC yields predictable outcomes.

CONCLUSION

Based on the results of this study, there is no significant difference in the success rate between nonsurgical primary and secondary RCTs performed using either the SC technique with CSBS or the WVC technique and ZOE sealer. The use of a CSBS with the SC technique appeared to be at least as reliable as the traditional WVC technique. The results of the 2- and 4-year follow-ups are consistent with those at 12 months and warrant further validation through larger randomized clinical trials.

AUTHOR CONTRIBUTIONS

Giulia Bardini: Conceptualization; methodology; investigation; writing—review and editing. **Montse Mercade Bellido:** Supervision; writing—review and editing. **Giampiero Rossi-Fedele:** Methodology; data curation; formal analysis (4 years recall). **Laura Casula:** Formal analysis (2 years recall). **Claudia Dettori:** Writing. **Francesca Ideo:** methodology. **Elisabetta Cotti:** Project administration; validation; writing—original draft preparation. All authors have contributed significantly and are in agreement with the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors deny any conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent was obtained from all individual study participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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