ORIGINAL ARTICLE

Intervention Effects on Post-Endodontic Pain in Trials Indexed Under Periodontitis: A ClinicalTrials.gov Aggregate-Data Analysis

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ABSTRACT

Background: Post-endodontic pain is a patient-important outcome, yet posted trial-registry results are difficult to compare because outcome scales, time points, and reporting structures vary.

Objective: This study aimed to estimate the magnitude and precision of intervention effects on postoperative pain and to characterize their temporal and multiplicity-adjusted patterns in eligible randomized endodontic trials.

Methods: ClinicalTrials.gov records from a frozen query for periodontitis studies with posted results were screened for randomized endodontic trials reporting arm-level pain means, dispersion, and denominators. Official API records were used to verify groups and outcomes. Raw mean differences and Hedges g with 95% confidence intervals were calculated without cross-trial pooling. Standard errors were converted to standard deviations where indicated, independent recruitment cohorts were combined within a trial, and multiplicity was controlled using Holm adjustment.

Results: Among 64 records, 11 contained pain-related outcomes and 4 endodontic trials were eligible. The trials enrolled 257 participants; 249 contributed to pain denominators. Nine of 18 non-pooled confidence intervals excluded zero, while 7 comparisons from 2 trials remained significant after Holm adjustment. Photobiomodulation produced lower pain than sham at 0, 6, 12, 24, and 72 hours. Cryotherapy produced lower pain than saline at 24 and 48 hours after adjustment. Estimates for occlusal reduction, GentleWave versus EndoActivator, and ibuprofen/acetaminophen versus ibuprofen were not robustly different.

Conclusion: Posted aggregate results revealed treatment- and time-specific signals rather than a common intervention effect. Verified extraction and multiplicity-aware non-pooled analysis improve interpretability, but clinical decisions require full publications and harmonized outcome definitions.

1. Introduction

Pain after root canal treatment is a patient-centered outcome with consequences beyond a single numerical score. During the first hours and days after treatment, pain can influence eating, sleep, rescue-analgesic use, satisfaction, and willingness to return for care. Its course is usually favorable, but intensity and timing vary with pulpal and periapical status, preoperative symptoms, instrumentation, apical tissue irritation, and the treatment strategy. Recent randomized trials demonstrate that changes in apical patency, shaping systems, and the selected definitive pulpal procedure can alter early pain or quality-of-life outcomes.[1-3] Post-endodontic pain should therefore be interpreted as a time-dependent patient-reported outcome rather than a fixed property of root canal treatment.

Measurement adds complexity. Visual analog and numerical scales convert subjective experience into analyzable values, but their units are not automatically interchangeable. A one-point difference on a 0-to-10 scale and a 10-mm difference on a 0-to-100 scale may occupy the same fraction of the scale while representing different distributions and clinical contexts. Repeated observations at 6, 24, 48, and 72 hours are correlated within participants rather than independent replications. Late observations may cluster near zero as inflammation resolves, producing a floor effect in which a standardized difference appears large although the absolute pain burden is small. An interpretable analysis must therefore preserve the native scale, report uncertainty, retain time-specific contrasts, and distinguish statistical separation from clinical importance.

Photobiomodulation is intended to modulate inflammatory and nociceptive activity through light-based exposure without changing the core mechanical procedure. Contemporary randomized trials have evaluated diode or low-level laser protocols in primary treatment and retreatment settings, with results that depend on wavelength, energy, application site, treatment stage, and comparator.[4-7] These studies support biological and clinical interest in the intervention while also showing why one device-specific result cannot be generalized to every photobiomodulation protocol.

Cryotherapy addresses pain through a different exposure: cooling the final irrigant, intracanal environment, or adjacent tissues. Recent randomized trials include applications during primary treatment, retreatment, and intraoral cooling, and they report effects that vary across baseline diagnoses, delivery procedures, comparators, and follow-up times.[8-12] This variability makes the temporal pattern important. A benefit concentrated at 24 or 48 hours is clinically and analytically different from an immediate effect or a late difference after both groups have approached the scale floor.

Irrigation activation, systemic or local analgesia, and procedural choices form additional pathways that can

influence recovery. Randomized trials of sonic, ultrasonic, laser-assisted, and finishing-file activation show that postoperative pain may differ with the activation method and clinical setting.[13-18] Trials of ibuprofen, sustained-release premedication, proteolytic anti-inflammatory treatment, corticosteroid or nonsteroidal premedication, and controlled-release aceclofenac likewise illustrate sensitivity to drug, dose, timing, and comparator.[19-23] Recent trials further show that foraminal enlargement, apical finishing size, instrumentation kinematics, glide-path systems, sealers, and shaping systems can modify or contextualize postoperative pain.[24-,30] The interventions represented in the supplied registry dataset are therefore scientifically related through the outcome of pain but do not constitute one exchangeable treatment class.

ClinicalTrials.gov provides structured study and posted-results modules that can be used to examine this evidence at the aggregate level. Their apparent structure does not eliminate the need for verification: outcome-group identifiers, labels, denominators, time frames, and dispersion types must be linked correctly. A mislabeled arm can reverse the meaning of a contrast, while interpreting a standard error as a standard deviation can materially narrow its confidence interval. The present study therefore treated each official registry JSON record as the numerical source and retained the supplied analytical file as an input requiring reconciliation.

The condition term periodontitis in the frozen registry query also required clinical clarification. It could retrieve periodontal disease, symptomatic apical periodontitis, mixed odontogenic infection, pulpal or periapical conditions, and records in which the term appeared only in an eligibility or descriptive field. The eligible records were randomized endodontic trials with reconstructable postoperative-pain outcomes, not a homogeneous sample of periodontal-disease trials. An interpretable effect profile also needed to avoid counting correlated time points as independent confirmations or pooling mechanistically and clinically dissimilar interventions merely because all outcomes measured pain.

The novelty of this study lies in constructing a source-verified, directionally harmonized, multiplicity-aware profile of posted post-endodontic pain outcomes from trials returned by a periodontitis registry query. The analysis integrates complete eligible pain time points, distinguishes standard errors from standard deviations, reconciles official arm identities, combines independent recruitment-period cohorts within study, and reports native-scale and standardized effects without cross-trial pooling. The primary aim was to estimate the magnitude and precision of intervention effects on postoperative pain within each eligible randomized endodontic trial. Secondary aims were to characterize the temporal pattern of pain, identify which comparisons remained supported after within-trial Holm adjustment, evaluate the influence of key data-derivation decisions, and define the limits of clinical interpretation from heterogeneous aggregate registry results.

2. Methods

Study design and reporting framework

This investigation was a cross-sectional secondary analysis of publicly posted aggregate trial results. The unit of scientific interpretation was the randomized within-trial comparison at a defined postoperative time point; the unit was not the individual participant and not a pooled intervention class. No new participants were recruited, no treatment was assigned by the investigators conducting this analysis, and no identifiable participant-level record was accessed. The study was organized as an Original Article and used relevant STROBE principles to report the data source, eligibility boundary, variables, quantitative methods, and interpretive constraints of registry-based observational analysis.[31] STROBE was adapted because the present work analyzed structured trial-result records rather than prospectively observing a clinical cohort. The study was not labeled a systematic review or meta-analysis because the search was a single frozen registry query and the included interventions were not judged exchangeable for pooled synthesis.

Before estimation, the analytical objective was specified as a non-pooled effect profile. This choice preserved the randomized comparison inside each source trial while avoiding a summary effect that would combine photobiomodulation, cryotherapy, occlusal reduction, irrigation activation, and analgesic regimens. The analysis retained both raw mean differences on the original pain scale and standardized mean differences for within-study interpretation. Statistical significance was treated as one component of evidence and was evaluated alongside effect magnitude, confidence intervals, absolute pain levels, timing, multiplicity, and the number of independent trials contributing supported findings. The reporting approach was therefore designed to answer where and when separation occurred rather than which intervention was universally superior.

Registry source, query, and data freeze

ClinicalTrials.gov served as the primary data source. The frozen query `AREA[ConditionSearch](periodontitis) AND AREA[HasResults]Y` was executed through application programming interface version 2 on 11 August 2025. The condition-search component preserved the provenance of the supplied analytical theme, and the results filter restricted retrieval to records with posted result modules. The API returned 64 records. The complete machine-readable response was retained as a frozen JSON file so that the screened corpus, record count, and source state could be reproduced even if registry entries were later updated. A separate query-count response was also retained to reconcile the number reported in the manuscript with the frozen full response.

For every eligible trial, an individual official JSON record was downloaded and retained. These records were treated as the authoritative source for study identity, allocation, intervention model, masking, enrollment, group identifiers, outcome definitions, measurement time frames, group denominators, means, and dispersion labels. Registry version dates were recorded. The author-supplied comma-separated file was preserved as an input source but was not treated as sufficient authority for final group labels or statistical descriptors. All analytical values used in the manuscript were traced back to one of the four retained official records: NCT05032612, NCT05722704, NCT04552132, or NCT03631433.

Eligibility criteria and screening

Screening proceeded in two stages. First, titles, conditions, brief descriptions, and posted outcome modules from all 64 records were searched for pain,

sensitivity, or discomfort terminology. Eleven candidate records contained at least one potentially relevant outcome. Second, each candidate's study design, clinical context, intervention, outcome definition, group structure, and numerical result fields were reviewed. A record was eligible when it was a randomized endodontic study with at least two analyzable groups and reported postoperative pain as an arm-level mean together with an analyzed denominator and a dispersion measure explicitly identified as a standard deviation or standard error. Both primary and secondary pain outcomes could be eligible because the objective was to characterize the complete posted postoperative trajectory within an otherwise eligible trial.

Records were excluded when the pain-related outcome concerned periodontal treatment rather than endodontic care, mixed dental infection without a comparable postoperative root-canal procedure, pain associated with local anesthesia or injection rather than recovery after endodontic treatment, chronic periodontal discomfort, or a non-comparable outcome structure that could not yield a valid arm-level mean difference. Seven of the eleven candidates were excluded on these grounds. The retained screening log lists each candidate and its principal reason for inclusion or exclusion. The resulting flow was therefore 64 records retrieved, 11 pain-term candidates reviewed in detail, and 4 randomized endodontic trials included. This eligibility boundary intentionally prioritized clinical and analytical comparability over the broad terminology of the original registry condition index.

No date, country, sponsor, or publication-status restriction was added after retrieval. Eligibility was determined from the posted record rather than from whether a corresponding journal article could be located. Trials were not excluded because their masking level differed or because they used different pain scales; those features were retained as study characteristics and informed the decision not to pool. The four included studies were conducted in the United States or United Arab Emirates, used parallel randomized designs, and together represented light-based, cooling, occlusal, irrigation-system, and pharmacological comparisons.

Outcome extraction and source verification

A structured extraction dataset was created at the arm-outcome-time level. For each posted pain outcome, the extracted fields were National Clinical Trial identifier, outcome index, registry designation as primary or secondary, outcome title and description, reported time frame, normalized time point in hours, group identifier, official group title, analyzed denominator, mean, spread, dispersion type, scale unit, and source filename. Lower scores represented less pain in every included outcome. Forty arm-level pain rows were retained before comparative aggregation. The extraction was programmatic but every retained group and outcome was checked against its official JSON structure to ensure that a value had not been paired with the wrong group or time point.

Verification resolved three interpretation-critical structures. First, the source analytical file represented the two NCT03631433 arms with a duplicated ibuprofen label. Official group metadata identified the comparison as ibuprofen/acetaminophen combination versus ibuprofen, so the official labels were used. Second, the NCT05722704 result module identified the 72-hour spreads as standard errors, whereas earlier time points were standard deviations. The dispersion type was therefore stored explicitly for every row rather than assumed from column position. Third, NCT04552132 posted the same 24-, 48-, 72-, and 96-hour outcome schedule for two independent recruitment periods. These cohorts were not treated as repeated observations from the same individuals and were combined within arm and common time point before the trial-level comparison was calculated.

The complete photobiomodulation trajectory in NCT05032612 was retained. The registry listed the 72-hour measurement as a primary outcome and 0-, 6-, 12-, and 24-hour measurements as secondary outcomes under a common pain construct. Restricting extraction to the primary field would have reduced a five-point trajectory to a single late observation and obscured early change. Because all five outcomes were posted for the same two randomized groups and used the same direction of interpretation, they were analyzed as time-specific contrasts and handled as one within-trial multiplicity family. Denominators were not summed across time: the pain-analysis population was counted once when describing distinct contributing participants.

Data harmonization and derived variables

Time frames were normalized to hours to support chronological ordering: immediate assessment was coded as 0 hours, the four-day survey as 96 hours, and explicitly reported hourly measurements retained their stated values. The native scale and outcome wording were preserved in the arm-level dataset. No attempt was made to transform all pain means to a common 0-to-10 metric because scale conversion would imply comparability that could not be guaranteed from the aggregate records. Standardization was performed only at the effect-estimate stage within a trial and time point, where the two compared groups shared the same measurement definition.

When a registry spread was labeled as a standard error, it was converted to a standard deviation using SD = SE multiplied by the square root of the analyzed group denominator. For NCT05722704 at 72 hours, this produced standard deviations of approximately 2.01 for cryotherapy, 0.98 for occlusal reduction, and 3.22 for saline from the posted standard errors of 0.45, 0.22, and 0.72 with n=20 per group. The conversion affects uncertainty rather than the arm mean. Treating these values as standard deviations would have understated dispersion and created overly narrow late confidence intervals; the explicit conversion was therefore retained in the verification log and sensitivity interpretation.

Independent recruitment-period cohorts within NCT04552132 were combined separately for each arm and time point. The combined mean was the sample-size-weighted mean across cohorts. The combined variance incorporated both within-cohort variability and the between-cohort difference in means, with degrees of freedom based on the total sample less one. This method preserved the information contributed by each independent cohort and avoided treating cohort-level means as equally weighted when their sample sizes differed. After aggregation, the analyzed denominators were 26 for GentleWave and 29 for EndoActivator at each common time point, for 55 distinct participants contributing pain data from an enrolled study population of 63.

Trial enrollment and pain-analysis denominators were reported separately. Registered enrollment was summed once across the four included trials, giving 257 participants. The contributing pain denominator was based on the distinct analyzed participants represented in the retained pain outcomes and totaled 249. Repeated time points did not increase this count. The distinction prevents a longitudinal trial with many measurements from appearing to contribute more participants than it actually enrolled. Missing participant-level observations, rescue medication use, baseline pain, and within-person covariance could not be reconstructed beyond what the aggregate registry modules reported.

$$SD = SE \times \sqrt{n}$$

Effect estimation and uncertainty

For each eligible comparison and time point, the raw mean difference was defined as the comparison-group mean minus the reference-group mean. The reference group was selected to keep the clinical direction explicit within each trial: PBM therapy was the reference for PBM sham, cryotherapy was the reference for occlusal reduction and saline, GentleWave was the reference for EndoActivator, and ibuprofen was the reference for the ibuprofen/acetaminophen combination. Because lower pain scores indicated a better outcome, a positive raw difference meant higher pain in the named comparison group and numerically favored the reference group. The raw difference and its 95% confidence interval were retained on the native scale.

Welch standard errors and Welch-Satterthwaite degrees of freedom were used for raw mean-difference inference so that equal group variances were not required. A two-sided p value was calculated for each time-specific mean difference. Standardized effects were expressed as Hedges g. The pooled within-time-point standard deviation was used to calculate Cohen's standardized difference, followed by the conventional small-sample correction factor to reduce bias. The sign convention matched the raw difference: positive Hedges g indicated higher pain in the comparison group and therefore favored the reference group numerically. Confidence intervals for Hedges g used its large-sample sampling variance. Both effect scales were retained because standardized values facilitate magnitude comparison within the effect plot, whereas raw differences preserve the absolute measurement context.

Eighteen study-comparison-time effects were estimated: one for NCT03631433, four for NCT04552132, five for NCT05032612, and eight for the two cryotherapy-referenced contrasts in the three-arm NCT05722704 trial. These estimates were not treated as 18 independent studies. To control the family of repeated comparisons inside each trial, unadjusted p values were ordered and adjusted using the sequential Holm procedure. Adjustment was applied within NCT identifier because the scientific interpretation concerned repeated or multiple comparisons arising from a common randomized study. A comparison was described as Holm-supported when its adjusted two-sided p value was below 0.05. Confidence intervals were shown without multiplicity adjustment, while open rings in Figure 2 identified the comparisons that remained significant after the Holm procedure.

No pooled mean difference or pooled standardized effect was calculated. The intervention mechanisms, clinical populations, comparators, native pain scales, assessment schedules, and repeated-measure structures were not sufficiently exchangeable to define a common causal estimand. A meta-regression or multivariable model was also not fitted: only four heterogeneous study clusters were available, participant-level covariates were absent, and repeated-time covariance could not be recovered. Adding a model under these conditions would produce unstable coefficients and misleading precision. The analysis instead emphasized within-trial randomization, effect magnitude, uncertainty, multiplicity, and temporal pattern.

$$MD = \bar{x}_c - \bar{x}_r$$

$$d = \mathrm{MD} \,/\, \mathrm{SD}_{\mathrm{pooled}}; \quad g = J \times d$$

$$J = 1 - 3 \,/\, [4(n_r + n_c) - 9]$$

Robustness and consistency checks

Three planned checks evaluated whether central interpretations depended on data handling. First, nominal confidence-interval results were compared with Holm-adjusted p-value results to determine how repeated testing changed the number of supported comparisons. Second, the NCT05722704 late estimates were recalculated after the standard-error-to-standard-deviation conversion and compared with the impression that would arise if the posted spreads were treated as standard deviations. Third, NCT04552132 cohort-specific rows were combined using sample-size and variance-aware formulas, and the aggregated time pattern was checked against the source cohorts to determine whether combination altered the qualitative result.

Numerical outputs were reconciled across the derived arm-level dataset, effect-estimate file, tables, figures, abstract, and main text. Representative Welch calculations were independently cross-checked in R version 4.5.3, while the full reproducible workflow was executed in Python. The frozen source records, analysis script, derived comma-separated files, verification log, figures, and session information were retained in the supplement. No observation or time point was removed on the basis of statistical significance.

Ethics and reproducibility

Ethical approval was granted by the CMHC Ethics Committee Indonesia (No. 007/CMHC/Ethics/08/202). The analysis used publicly accessible aggregate registry results and did not access names, contact information, individual dates, or other identifiable participant data. Additional participant consent was therefore not applicable to this secondary aggregate-data analysis. Ethics approval, consent applicability, and data availability were recorded as separate metadata rather than inferred from one another.

Reproducibility materials accompany the case package. They include the full frozen 64-record query response, four official trial JSON records, the candidate screening log, source and claim ledgers, verified arm-level pain data, trial-characteristics data, all non-pooled effect estimates, software and session information, the executable analysis script, and publication figures. These materials allow the reported counts and estimates to be traced from registry field to manuscript statement.

3. Results

Study selection and trial characteristics

The frozen query returned 64 records with posted results. Eleven records contained a pain-, sensitivity-, or discomfort-related outcome that warranted detailed screening. Four met the predefined randomized endodontic postoperative-pain criteria, whereas seven concerned periodontal procedures, mixed infection, pulpal anesthesia or injection pain, chronic periodontal discomfort, or an outcome structure that could not support the planned arm-level comparison. The included records were NCT05032612, NCT05722704, NCT04552132, and NCT03631433. Thus, the registry flow was 64 retrieved records, 11 pain-term candidates, and 4 eligible trials, as detailed in Figure 1.

All four included studies used randomized parallel-group designs and had completed status in the retained registry records. Three trials were conducted in the United States, including the GentleWave-EndoActivator trial, and the cryotherapy trial was conducted in the United Arab Emirates. Masking ranged from none in NCT04552132 to single masking in NCT05032612, double masking in NCT05722704, and triple masking in NCT03631433. Follow-up ranged from immediate assessment after treatment to a four-day postoperative survey. The trials enrolled 257 participants in total; 249 distinct participants contributed to the analyzed pain denominators as detailed in Table 1.

The intervention structures differed materially. NCT05032612 randomized 32 participants to photobiomodulation therapy or sham and reported pain for 17 and 15 participants, respectively. NCT05722704 enrolled 60 participants and allocated 20 each to cryotherapy, occlusal reduction, or saline. NCT04552132 enrolled 63 participants; after combining two recruitment-period cohorts, 26 GentleWave and 29 EndoActivator participants contributed to pain analyses. NCT03631433 enrolled and analyzed 102 participants, with 49 in the ibuprofen group and 53 in the ibuprofen/acetaminophen combination group. These differences in intervention, masking, scale, and timing supported presentation as separate randomized comparisons rather than as one treatment network.

Overall pattern of non-pooled effects

Forty verified arm-level pain rows yielded 18 non-pooled study-comparison-time effects after the independent NCT04552132 recruitment cohorts were combined within arm and time point. Nine Hedges g confidence intervals excluded zero before multiplicity was considered. Seven comparisons remained significant after within-trial Holm adjustment, and all seven arose from two trials: five photobiomodulation-sham comparisons in NCT05032612 and two saline-cryotherapy comparisons in NCT05722704. No adjusted signal arose from the GentleWave-EndoActivator or ibuprofen/acetaminophen-ibuprofen comparisons. All 18 non-pooled estimates are displayed in Figure 2, and the seven Holm-supported estimates are detailed in Table 2.

The direction of the standardized effects was internally consistent with the native means. Positive values in Figure 2 indicate higher pain in the named comparison group and numerically favor the reference group. The observed range extended from g=-0.07 for the ibuprofen/acetaminophen combination versus ibuprofen to g=1.42 for PBM sham versus PBM therapy at 12 hours. The distribution did not support one common intervention effect: estimates clustered by trial and time, and the largest supported values were concentrated in comparisons against sham or saline rather than distributed across all active comparators.

Table 1. Characteristics of the eligible randomized endodontic trials.

Trial	Setting and design	Comparison	Enrolled / pain n	Pain assessment
NCT05032612	United States; randomized, single-masked	PBM therapy vs sham	32 / 32	0, 6, 12, 24, 72 h
NCT05722704	United Arab Emirates; randomized, double-masked	Cryotherapy vs occlusal reduction vs saline	60 / 60	6, 24, 48, 72 h
NCT04552132	United States; randomized, open-label	GentleWave vs EndoActivator	63 / 55	24, 48, 72, 96 h
NCT03631433	United States; randomized, triple-masked	Ibuprofen vs ibuprofen/acetaminophen	102 / 102	4-day survey

PBM, photobiomodulation; pain n counts distinct participants contributing to the pain outcome and is not summed across repeated me asurements.

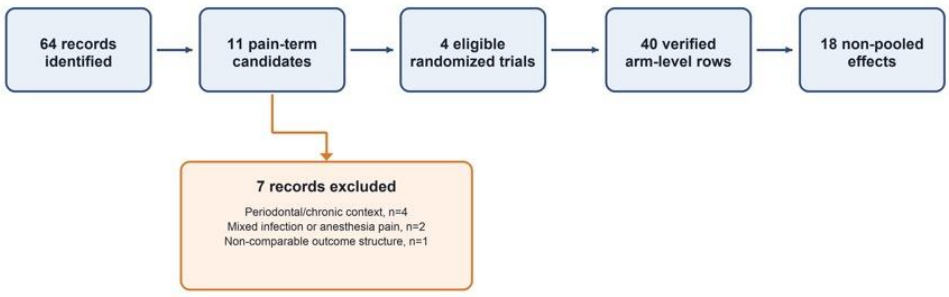

Figure 1. Selection and analytical flow from the frozen registry query to the final non-pooled effect profile. Counts are derived from the retained query response, screening log, verified arm-level dataset, and effect-estimate file.

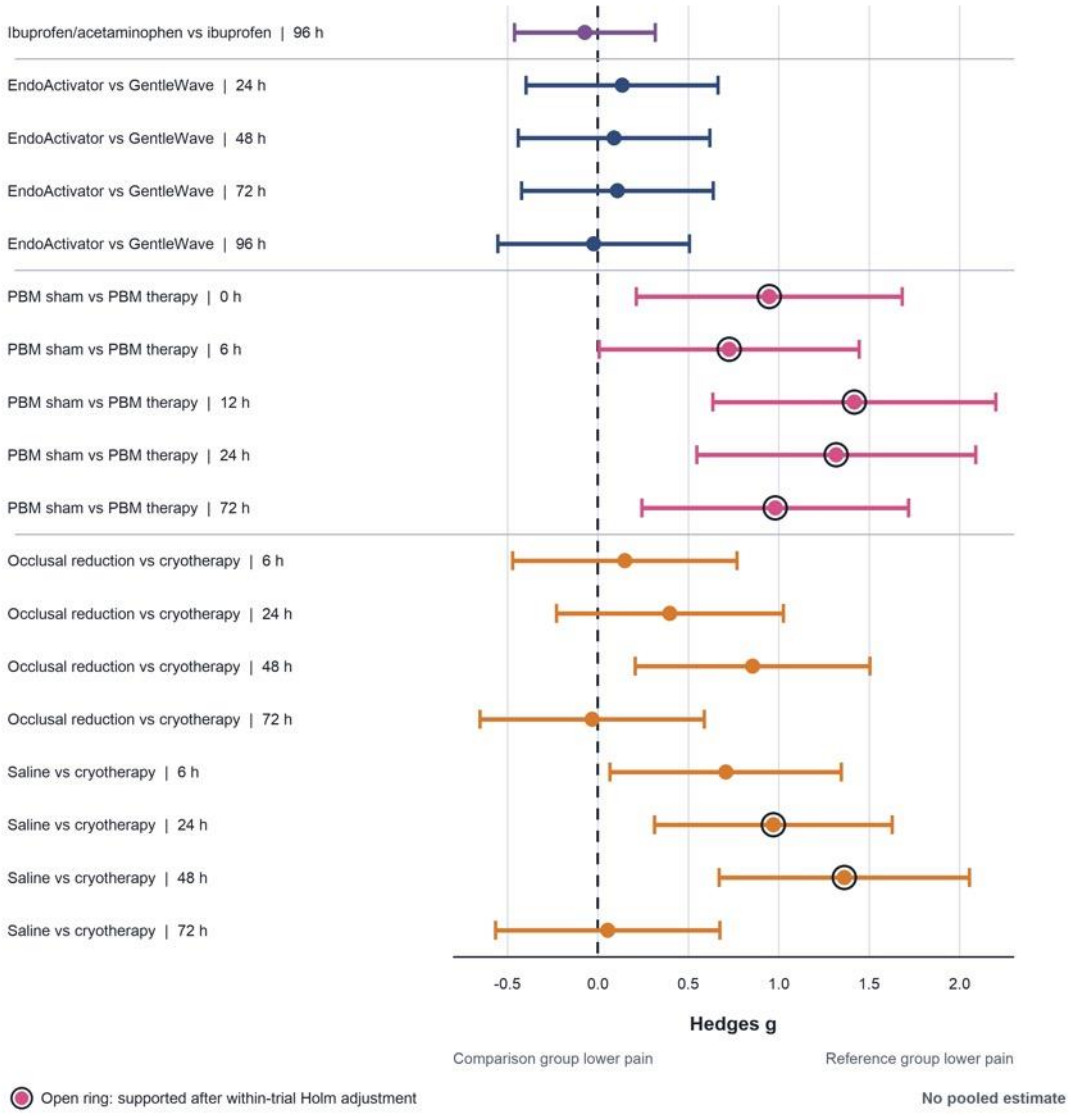

Figure 2. Non-pooled within-trial effects on post-endodontic pain. Points show Hedges g and bars show 95% confidence intervals. Positive values indicate higher pain in the named comparison group and favor the reference group. Open rings identify compari sons remaining significant after within-trial Holm adjustment. No pooled estimate was calculated.

Table 2. Estimates remaining statistically supported after within-trial Holm adjustment.

Trial	Time	Comparison	Raw MD (95% CI)	Hedges g (95% CI)	Holm p
NCT05032612	0 hours	PBM sham vs PBM therapy	2.19 (0.53 to 3.85)	0.95 (0.21 to 1.68)	0.035
NCT05032612	6 hours	PBM sham vs PBM therapy	1.92 (0.04 to 3.80)	0.73 (0.01 to 1.45)	0.045
NCT05032612	12 hours	PBM sham vs PBM therapy	2.57 (1.19 to 3.95)	1.42 (0.64 to 2.20)	0.005
NCT05032612	24 hours	PBM sham vs PBM therapy	1.17 (0.49 to 1.85)	1.32 (0.55 to 2.09)	0.008
NCT05032612	72 hours	PBM sham vs PBM therapy	0.33 (0.06 to 0.60)	0.98 (0.24 to 1.72)	0.037
NCT05722704	24 hours	Saline vs Cryotherapy	1.50 (0.52 to 2.48)	0.97 (0.31 to 1.63)	0.026
NCT05722704	48 hours	Saline vs Cryotherapy	1.95 (1.04 to 2.86)	1.36 (0.67 to 2.05)	0.001

CI, confidence interval; MD, comparison-minus-reference mean difference. Positive estimates indicate higher pain in the comparison group. Values are generated directly from the verified effect-estimate dataset.

Photobiomodulation trial

In NCT05032612, the photobiomodulation group had lower mean pain than the sham group at every posted time point. Immediately after treatment, means were 3.94 for therapy and 6.13 for sham, giving a raw difference of 2.19 points and Hedges g=0.95 (95% CI 0.21 to 1.68). At 6 hours, means were 1.94 and 3.86, respectively; the 1.92-point difference corresponded to g=0.73 (95% CI 0.01 to 1.45). At 12 hours, the therapy mean had declined to 0.76 compared with 3.33 under sham. This was the largest standardized separation, with a 2.57-point raw difference and g=1.42 (95% CI 0.64 to 2.20). The complete multiplicity-supported PBM estimates are detailed in Table 2.

The separation persisted as absolute scores declined. At 24 hours, the therapy and sham means were 0.23 and 1.40, a 1.17-point difference with g=1.32 (95% CI 0.55 to 2.09). At 72 hours, the therapy mean was 0 and the sham mean was 0.33, producing a smaller native-scale difference of 0.33 points but g=0.98 (95% CI 0.24 to 1.72). All five comparisons remained significant after Holm adjustment within NCT05032612. The late result demonstrates the importance of considering absolute and standardized scales together: the standardized effect remained sizable because variability was limited, yet both groups were close to the no-pain floor and the absolute difference was small.

Cryotherapy, occlusal reduction, and saline trial

In NCT05722704, mean pain declined in all three groups between 6 and 72 hours. At 6 hours, means were 1.85 for cryotherapy, 2.15 for occlusal reduction, and 3.65 for saline. Occlusal reduction differed from cryotherapy by 0.30 points (g=0.15, 95% CI -0.47 to 0.77). Saline differed from cryotherapy by 1.80 points (g=0.71, 95% CI 0.07 to 1.35); its nominal confidence interval excluded zero, but the comparison did not remain significant after adjustment across the trial's eight estimates.

At 24 hours, mean pain was 0.70 with cryotherapy, 1.20 with occlusal reduction, and 2.20 with saline. The occlusal-reduction contrast remained imprecise (raw difference 0.50; g=0.40, 95% CI -0.23 to 1.03). Saline showed higher pain than cryotherapy by 1.50 points, corresponding to g=0.97 (95% CI 0.31 to 1.63) and a Holm-adjusted p value of 0.026. At 48 hours, means were 0.25, 1.20, and 2.20, respectively. Occlusal reduction differed from cryotherapy by 0.95 points (g=0.86, 95% CI 0.21 to 1.50), but its adjusted p value was 0.057 and therefore did not meet the prespecified threshold. Saline differed from cryotherapy by 1.95 points, with g=1.36 (95% CI 0.67 to 2.05) and an adjusted p value of 0.001. These group means and their temporal pattern are displayed in Figure 3, while the supported saline contrasts are detailed in Table 2.

At 72 hours, reported means were low in every group: 0.10 for cryotherapy, 0.05 for occlusal reduction, and 0.25 for saline. After the posted standard errors were converted to standard deviations, both contrasts were imprecise and near null. Occlusal reduction versus cryotherapy yielded a raw difference of -0.05 and g=-0.03 (95% CI -0.65 to 0.59); saline versus cryotherapy yielded a raw difference of 0.15 and g=0.05 (95% CI -0.57 to 0.67). The supported cryotherapy signal was therefore concentrated at 24 and 48 hours against saline. It was not evident against occlusal reduction after multiplicity adjustment and did not persist as a precise late separation at 72 hours.

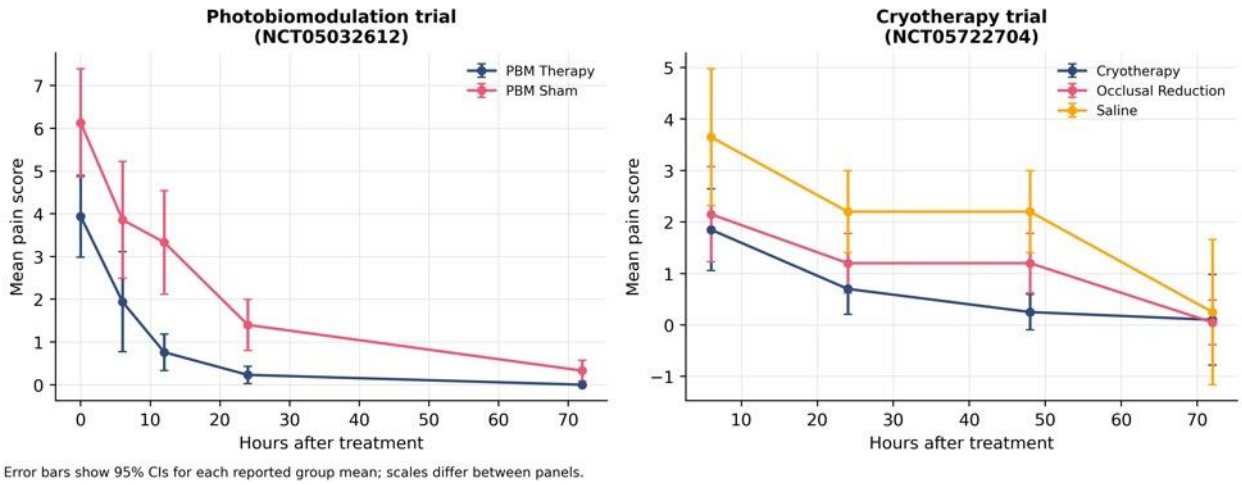

Figure 3. Posted group-mean pain trajectories for the photobiomodulation and cryotherapy trials. Error bars are 95% confidence intervals for each mean. Pain scales differ between panels; the figure is descriptive and does not pool trials.

Irrigation-system and analgesic comparisons

After aggregation of the two recruitment-period cohorts in NCT04552132, GentleWave and EndoActivator showed similar pain at all four time points. At 24 hours, means were approximately 13.73 and 16.60 on the posted scale, with g=0.13 (95% CI -0.40 to 0.66). At 48 hours, means were 9.50 and 10.93, with g=0.09 (95% CI -0.44 to 0.62). At 72 hours, means were 5.37 and 6.60, with g=0.11 (95% CI -0.42 to 0.64). At 96 hours, means were 5.44 and 5.14, and the direction reversed slightly (g=-0.02, 95% CI -0.55 to 0.51). All four confidence intervals included zero, Holm-adjusted p values were 1.00, and both groups exhibited declining pain over time.

In NCT03631433, the four-day Heft-Parker Visual Analog Scale mean was 63 with ibuprofen and 60 with the ibuprofen/acetaminophen combination. The combination-minus-ibuprofen raw difference was -3 points (95% CI -19.31 to 13.31), corresponding to g=-0.07 (95% CI -0.46 to 0.32; p=0.716). The aggregate registry result was therefore compatible with effects ranging from a modest advantage for the combination to a modest advantage for ibuprofen alone. It did not demonstrate a precise difference between regimens in this trial context.

Robustness and numerical reconciliation

Multiplicity adjustment reduced the count of statistically supported comparisons from nine confidence intervals excluding zero to seven Holm-significant effects. The five photobiomodulation contrasts and the 24- and 48-hour saline-versus-cryotherapy contrasts retained support. The nominal saline contrast at 6 hours and occlusal-reduction contrast at 48 hours did not. Thus, the principal qualitative interpretation was stable—signals remained concentrated in photobiomodulation and selected cryotherapy comparisons—but the adjusted

results provided a more conservative count and prevented correlated time points from being read as independent confirmations.

The dispersion check materially changed the appearance of NCT05722704 at 72 hours. Converting standard errors to standard deviations widened the late confidence intervals and yielded near-null, imprecise effects, consistent with the low absolute means and limited ability to distinguish groups. Aggregating NCT04552132 recruitment-period cohorts reduced eight cohort-specific comparison rows to four trial-level time-point estimates. The combined values maintained the same small, null pattern and did not create or conceal a supported difference. Representative calculations matched the independent R cross-check, and all abstract, table, figure, and text counts were reconciled with the final derived files.

4. Discussion

Principal findings

This source-verified analysis found that posted registry evidence on post-endodontic pain was intervention-specific and time-specific rather than consistent with a common treatment effect. Five photobiomodulation-versus-sham contrasts and two cryotherapy-versus-saline contrasts remained supported after within-trial Holm adjustment. The photobiomodulation separation was observed from immediate assessment through 72 hours, although the absolute late difference was small because both groups approached the scale floor. Cryotherapy separated most clearly from saline at 24 and 48 hours, but not from occlusal reduction after multiplicity control, and the properly handled 72-hour estimates were imprecise and near null. GentleWave versus EndoActivator and ibuprofen/acetaminophen versus ibuprofen showed small or imprecise differences. These findings directly answer the study aim at the within-trial level and do not support pooling or a cross-intervention ranking.

The adjusted count is important. Nine confidence intervals excluded zero, but two nominal findings did not survive the trial-level Holm procedure. Seven supported comparisons might initially appear to represent a broad evidence base; in fact, they arose from only two randomized trials, and five were repeated time points from one small photobiomodulation study. The number of statistically supported rows therefore cannot be equated with the number of independent replications. The most defensible interpretation is that the registry contains coherent within-trial signals that warrant confirmation, not seven separate demonstrations of clinical efficacy.

Contribution of the registry-verification approach

The study's contribution is methodological as well as clinical. Public trial registries can expand access to outcome data, but their structured appearance may encourage analysts to treat exported rows as analysis-ready. The present workflow shows why group identity, dispersion type, time-point designation, denominator, and cohort structure must be verified before estimation. The official NCT03631433 metadata changed the meaning of a duplicated source label; the NCT05722704 dispersion field changed late uncertainty; secondary NCT05032612 outcomes revealed the clinically informative early trajectory; and the NCT04552132 cohort structure required variance-aware aggregation. None of these operations altered an observed arm mean to improve a result. They restored the intended linkage between posted fields and the estimand.

This approach complements, rather than replaces, journal publications. ClinicalTrials.gov was created to make structured trial information and results more accessible, and registry records can contain outcomes or detail not emphasized in articles. At the same time, documented discrepancies between registry and publication results mean that neither source should automatically be assumed complete. A robust evidence workflow should reconcile the registry with full reports and protocols when those are available. The present analysis deliberately bounded its claims to verified posted aggregate data and preserved the frozen records so that future investigators can reproduce the exact source state.

Interpretation of photobiomodulation

The photobiomodulation trial showed the most temporally consistent separation. Therapy-group pain was lower than sham immediately and at 6, 12, 24, and 72 hours, with standardized effects ranging from moderate to large. The largest native difference occurred at 12 hours, when the sham mean remained above three points and the therapy mean was below one. This timing is clinically plausible for an adjunct intended to modulate early inflammatory and nociceptive processes. Photobiomodulation has been proposed to influence cellular signaling, microcirculation, inflammatory mediator activity, and neural sensitivity, but the aggregate registry result cannot identify which mechanism, if any, produced the observed separation. It establishes a treatment-associated pattern within one randomized trial, not a biological mediation pathway.

The direction is consistent with recent randomized trials reporting reduced postoperative pain under selected diode, low-level laser, and combined laser-photobiomodulation protocols.[4–7] Such heterogeneity matters because photobiomodulation is not a single standardized exposure. An effect observed under one device and protocol cannot be transferred automatically to all light-based regimens. Replication should specify wavelength, output, dose, exposure schedule, application location, masking, and rescue-analgesic use at predefined times.

The late result illustrates the difference between statistical and clinical magnitude. At 72 hours, the therapy mean was zero and the sham mean was 0.33 on a 0-to-10 scale. The standardized effect remained close to one because within-group dispersion was small, but the absolute group difference was one-third of a scale point and both means indicated little pain. A large Hedges g in a floor-limited distribution should not be interpreted as a large residual burden avoided. For decision making, the earlier absolute differences may be more relevant than the late standardized value. Future trials should report a prospectively selected minimally important difference, the proportion of participants with clinically meaningful pain, rescue medication, sleep or function, and adverse effects, rather than relying only on group means.

Interpretation of cryotherapy and occlusal reduction

Cryotherapy produced its clearest adjusted separation from saline at 24 and 48 hours. This pattern is compatible with a time-limited effect during the period when

postoperative inflammation and apical tissue sensitivity remain active. Cooling may reduce local metabolic activity, edema, inflammatory signaling, and neural conduction, but the magnitude and duration of tissue cooling depend on irrigant temperature, volume, delivery method, canal anatomy, treatment duration, and the interval between intervention and pain measurement. Recent randomized studies in primary treatment, retreatment, and intraoral applications report both favorable and context-dependent patterns.[8-12] The present registry profile therefore supports a trial-specific early signal rather than a universal cryotherapy effect.

The comparison with occlusal reduction adds nuance. At 48 hours, occlusal reduction had higher pain than cryotherapy with a nominal confidence interval excluding zero, but the adjusted p value was 0.057. This result is neither proof of equivalence nor evidence that the interventions have identical effects. It indicates that the available three-arm aggregate data did not provide robust separation after accounting for the trial's multiple comparisons. Evidence on occlusal reduction itself has been variable, as reflected in systematic-review findings. Mechanical unloading may matter more in patients with particular preoperative occlusal contacts, percussion sensitivity, or apical inflammation, but those participant-level modifiers were unavailable here.

The saline comparator also deserves careful interpretation. Saline functioned as the reference alternative within the source trial, but the registry record alone does not provide a complete mechanistic decomposition of cooling, irrigation volume, contact time, operator behavior, and contextual care. The 24- and 48-hour differences support a comparative signal in that trial. They do not establish that cryotherapy will outperform every active pain-control approach or that a particular cooling protocol should be adopted universally. Confirmation requires adequately masked studies with standardized temperatures, delivery procedures, baseline pain stratification, prespecified primary time points, and consistent reporting of analgesic rescue and adverse events.

Irrigation-system findings

GentleWave and EndoActivator showed closely overlapping aggregate pain trajectories from 24 to 96 hours. Every standardized estimate was close to zero, and all confidence intervals were wide enough to include clinically different possibilities in either direction. Recent randomized trials of sonic, ultrasonic, laser-assisted, and finishing-file activation likewise show that pain responses depend on the activation system, baseline diagnosis, and treatment protocol.[13-18] Similar pain does not imply identical cleaning performance, healing, cost, efficiency, or long-term outcomes.

The cohort aggregation strengthened interpretability by converting two recruitment-period result sets into one trial-level estimate at each common time point. The combined means preserved the downward trajectory and the small group differences. Nevertheless, aggregate combination cannot adjust for changes in clinical practice, operator experience, baseline case mix, or other characteristics that may have differed between recruitment periods. Because the source record provided no participant-level covariance or covariates, a repeated-measures or adjusted longitudinal model was not possible. The null pattern should therefore be understood as absence of a clearly resolved group difference in the posted aggregate data, not proof of therapeutic equivalence.

Analgesic comparison

The ibuprofen/acetaminophen combination trial produced a near-null four-day aggregate estimate. The confidence interval was wide and included advantages for either regimen, so the result should not be interpreted as demonstrating equivalence. Pharmacological comparisons are especially sensitive to dose, administration timing, baseline pain, rescue medication, adherence, treatment completion, formulation, and the way pain is summarized over time. A four-day survey mean may integrate experiences that differ from a single peak-pain or early-time assessment. Without participant-level trajectories, it is not possible to determine whether subgroups or particular postoperative periods differed.

The wider literature illustrates this contextual dependence. Recent randomized trials have evaluated local versus systemic ibuprofen, sustained-release ibuprofen premedication, trypsin-chymotrypsin, piroxicam or prednisolone premedication, and controlled-release aceclofenac.[19-23] Their differing populations, doses, administration schedules, and endpoints reinforce that one near-null four-day registry estimate cannot be generalized to all postoperative analgesic strategies.

Statistical significance, clinical importance, and time

The analysis reinforces that p values, standardized effects, and clinical importance answer different questions. A confidence interval excluding zero indicates statistical separation under the model and source assumptions. Hedges g expresses that separation relative to within-group variability. Neither measure defines how much change patients consider worthwhile. Across the included trials, pain scales differed and no common minimally important threshold was prospectively available in the posted aggregate fields. Consequently, a value of g=1 in one trial cannot be translated directly into a uniform clinical recommendation across interventions or scales.

Time changes the meaning of an effect. Early after treatment, a difference of one or two points may coincide with meaningful symptoms and analgesic need. Later, the same standardized magnitude may arise from very small absolute differences near zero. Conversely, a non-significant late comparison may simply reflect that both groups recovered well. Figure 3 provides temporal context by showing whether an intervention shifts the entire recovery curve, accelerates decline, produces a transient separation, or differs only after most pain has resolved. The PBM pattern suggested separation throughout the posted course, while the cryotherapy pattern was most distinct at 24 and 48 hours against saline. These are different temporal profiles and should not be compressed into one efficacy label.

Multiplicity adjustment also changes the evidentiary interpretation. Repeated testing increases the probability that at least one nominally significant result will occur even when no true difference exists. The Holm procedure retained the strongest signals without requiring an assumption that all time points were independent. Because the exact within-person correlations were unavailable, the adjustment was intentionally conservative at the trial level.

Reporting both nominal confidence intervals and adjusted significance allows readers to see magnitude and precision while recognizing that a series of correlated rows is not equivalent to multiple independent trials.

Clinical and research implications

For clinical practice, the present results identify intervention-specific signals that may inform questions for future confirmation rather than immediate universal protocols. Photobiomodulation showed a consistent within-trial pattern, and cryotherapy showed selected early advantages over saline. Neither result establishes superiority over all active alternatives. Decisions should also consider feasibility, equipment, training, cost, treatment workflow, patient preferences, contraindications, adverse events, and the certainty of the wider evidence. The registry did not provide enough harmonized information to compare these dimensions, and the analysis did not evaluate long-term healing or procedural effectiveness.

Future endodontic pain trials would benefit from a core outcome strategy. Investigators should define a primary pain scale and time point prospectively, justify a minimally important difference, report the full temporal trajectory, and include rescue analgesic use, function, sleep, satisfaction, and adverse events when relevant. Baseline pain and diagnosis should be described consistently, and randomized groups should be linked identically across registry, protocol, statistical analysis plan, and publication. Repeated-measures analyses should account for within-person correlation and report treatment-by-time effects where scientifically appropriate. These steps would permit more informative synthesis and reduce reliance on isolated p values. Contemporary randomized evidence also indicates that apical enlargement, finishing size, kinematics, glide-path preparation, sealer choice, and shaping system should be reported as potential procedural determinants rather than treated as incidental details.[24-30]

Registry reporting can also be strengthened. Clear dispersion labels, explicit scale ranges, stable group titles, analyzed denominators at every outcome, and links to protocols and publications would reduce ambiguity. When a trial contains multiple recruitment cohorts or outcome modules, the relationship between them should be stated directly. Machine-readable result formats are valuable, but automated extraction should be followed by validation rules that flag duplicated labels, mixed standard errors and standard deviations, inconsistent denominators, and repeated time points. Publishing reproducible derived data and code allows corrections to be audited without obscuring the original registry record.

Strengths and limitations

The study has several strengths. The query and date were frozen; all 64 returned records were retained; screening criteria and exclusions were documented; and every included numerical result was verified against an official JSON record. Raw source files remained unchanged, while derived data, transformation rules, effect calculations, and software information were preserved. The analysis reported native and standardized effects, confidence intervals, trial-level multiplicity adjustment, explicit non-pooling, and an independent statistical cross-check. It distinguished registered enrollment from unique pain denominators and avoided double-counting repeated measurements as additional participants. Tables 1-2 and Figures 1-3 were constructed directly from the reconciled machine-readable outputs and are explicitly linked to the relevant Results narrative.

The constraints are equally important. The search was limited to records indexed by the specified periodontitis condition query and may omit relevant endodontic trials indexed under other terms. Screening was designed for this registry corpus and should not be interpreted as a comprehensive systematic literature search. Only four heterogeneous randomized trials met the aggregate numerical criteria. Supported findings arose from two trials, and five time-specific results came from one small photobiomodulation study. Aggregate data prevented adjustment for baseline pain, diagnosis, operator, tooth characteristics, analgesic use, or other potential effect modifiers. Within-person covariance was unavailable, precluding a repeated-measures model and limiting interpretation of the temporal estimates as a correlated series.

Outcome scales and schedules differed, and minimally important thresholds were not harmonized. Full risk-of-bias assessment, protocol-publication reconciliation, and evaluation of selective reporting were outside the retained registry dataset. Masking ranged from none to triple masking, which can influence subjective pain reporting. The analysis depended on sponsor-entered registry fields and could verify their internal structure but not independently audit the underlying participant measurements. Welch and Hedges g calculations assume that posted means, denominators, and dispersion measures accurately summarize their groups. The large-sample variance used for standardized-effect confidence intervals may be approximate in small samples.

Non-pooling is both a strength and a limitation. It protects against a clinically incoherent summary effect, but it means the study cannot provide a single estimate for guideline development or formal treatment ranking. The within-trial Holm procedure addresses multiplicity but does not recover the correlation between repeated observations. Results near the scale floor require special caution, and absence of a significant difference should not be read as equivalence. These conditions narrow the appropriate conclusion to reproducible trial-specific signals and methodological lessons for registry analysis.

Overall interpretation

Taken together, the results support a calibrated interpretation. The registry evidence is most persuasive where a coherent temporal pattern, meaningful absolute separation, and multiplicity-adjusted support coincide. Photobiomodulation met those criteria at several early time points in one randomized trial. Cryotherapy met them at 24 and 48 hours against saline in one three-arm trial. The remaining comparisons were small, imprecise, or unsupported after adjustment. The analysis therefore advances understanding not by declaring a winning intervention, but by locating credible signals, showing how source verification changes uncertainty, and defining what the available aggregate records cannot establish.

5. Conclusion

A frozen ClinicalTrials.gov query indexed under periodontitis identified four randomized endodontic trials with analyzable postoperative pain results. Source verification and non-pooled estimation showed distinct

within-trial temporal patterns. Photobiomodulation was associated with lower pain than sham at five assessments from immediate follow-up through 72 hours, although the late absolute difference was small because pain approached the scale floor. Cryotherapy was associated with lower pain than saline at 24 and 48 hours after within-trial Holm adjustment, while separation from occlusal reduction was not robust and 72-hour comparisons were imprecise after standard errors were correctly converted to standard deviations. GentleWave versus EndoActivator and ibuprofen/acetaminophen versus ibuprofen did not show clearly resolved aggregate differences. These findings do not support a pooled intervention effect or universal treatment ranking. They demonstrate the value of verifying registry group identity, dispersion type, denominator, time structure, and cohort composition before clinical interpretation. Confirmation in adequately powered trials with harmonized pain outcomes, predefined clinically important thresholds, repeated-measures analysis, rescue-medication reporting, and consistent registry-publication linkage is required before the identified signals can guide broad practice recommendations.

Declarations

Ethics approval: Ethical approval was granted by the CMHC Ethics Committee Indonesia (No. 007/CMHC/Ethics/08/2025).

Consent to participate: Not applicable because this study was a secondary analysis of publicly available aggregate records and involved no identifiable participant-level data.

Data and code availability: Source records are publicly available through ClinicalTrials.gov under NCT05032612, NCT05722704, NCT04552132, and NCT03631433. Derived datasets, verification logs, and analysis code accompany the submission package.

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