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Cold Atmospheric Plasma for Partial-Thickness Burns: Faster Epithelialization and Less Pain with Modern Dressings: A Randomized Clinical Trial

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Abstract

Background: Partial-thickness burns remain a substantial clinical and service burden, with wide variation in practice and outcomes across settings. Evidence for cold atmospheric plasma (CAP) as an adjuvant to modern dressings is promising but limited, and its effects on healing trajectories and pain in acute burns are not well-defined

Purpose: This study aimed to test whether adding CAP to modern dressings accelerates wound healing and reduces procedural pain compared with dressings alone among adults with second-degree burns

Methods: In a two-arm, assessor-blinded randomized trial at Donghae Dong-in Hospital, Republic of Korea (February–March 2025), adults ≥18 years with partial-thickness burns presenting within 72 hours were randomized to CAP + modern dressing or dressing alone. Forty-one were randomized; 36 contributed to the primary analysis. CAP was applied 3×week for 5–8 minutes before dressing placement. The primary outcome was the percent change in wound area over 28 days. Secondary outcomes were time to complete epithelialization and pain during dressing change (VAS 0–10). Analyses used GLM repeated-measures ANCOVA (covariates: %TBSA, age) and Cox regression

Findings: Among 36 analyzed participants (balanced baseline; median %TBSA 5%), CAP accelerated wound-area reduction versus control (Group×Time $p<0.001$; $\eta p^2=0.25$). By Day 28, CAP achieved a 17% greater reduction (adjusted Δ -17%, 95% CI −23 to −11). Pain declined faster with CAP (adjusted Δ −1.5 at Day 14; -1.9 at Day 28). Time to complete epithelialization was shorter with CAP (median 14 vs 21 days; adjusted HR 2.12, 95% CI 1.12–4.01). Effects were directionally consistent across prespecified sensitivity analyses.

Conclusion: Adding CAP to modern dressings improved healing trajectories, reduced procedural pain, and shortened time to epithelialization in adults with partial-thickness burns. Finding support protocolized adoption in capable units and motivating multicentre trials with scar, microbiological, and economic endpoints

Keywords: burns; wound healing; plasma gases; adult

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Introduction

Partial-thickness (second-degree) burns are common and demand rapid re-epithelialization, infection control, pain relief, and scar prevention. Nature Reviews Disease Primers highlights persistent variation in practice despite advances in dressings (Jeschke et al., 2020). Contemporary guidance notes that outcomes remain inconsistent across products and settings (Ji et al., 2024).

Global burn mortality has fallen, yet the burden of disability and resource use remains high (World Health Organization, 2023). Even small-to-moderate burns can cause chronic pain, functional loss, and reduced quality of life through delayed healing and hypertrophic scarring (Chiang et al., 2016). The prevalence of wounds in Asia was 32.1% (Burhan et al., 2025). Recent global estimates reaffirm substantial injury-related DALYs attributable to burns, particularly in low- and middle-income regions (Huang et al., 2025).

Keywords: burns; wound healing; plasma gases; adult

Comparative studies on partial-thickness burn therapies are often single-centre, underpowered, and short in follow-up (Jiang et al., 2017). Reviews frequently report inconsistent endpoints and inadequate handling of repeated observations over time. (Richards et al., 2025). Failure to adjust for key covariates such as %TBSA, age, and wound location further limits causal inference (Palmieri et al., 2017).

Modern dressings frequently outperform silver sulfadiazine for pain and time to healing, but effect sizes vary, and head-to-head trials are limited. (Nímia et al., 2019). Evidence on adjuvants that modulate both bioburden and inflammation across serial assessments is sparse (Kagan et al., 2020). Patient-centred outcomes such as the trajectory of wound-area reduction, time to complete epithelialization, and early scar risk remain incompletely characterized. (Lou et al., 2025).

At the bedside, clinicians must balance antimicrobial control, exudate management, comfort, cost, and frequency of dressing changes (Holbert et al., 2024). Implementation work shows barriers to adopting adjunctive modalities, including logistics, training, and uncertainty about which patients benefit most. (Jeschke et al., 2020). Pragmatic, statistically rigorous designs are needed to support protocolized pathways in routine care (UpToDate, 2025).

Cold atmospheric plasma (CAP) offers non-thermal antimicrobial and pro-healing effects relevant to second-degree burns. (Murali et al., 2024). Early trials suggest CAP can reduce bioburden and modulate inflammation, but clinical evidence in acute burns is preliminary and heterogeneous (Raissi-Dehkordi et al., 2025). This study evaluates CAP as an adjuvant to modern dressings using a longitudinal GLM repeated-measures (mixed ANOVA) with covariate adjustment for %TBSA and age to estimate treatment-by-time effects on healing and pain.

Method

Study Design and Setting

This was a two-arm, parallel-group, assessor-blinded, randomized clinical trial with repeated measures over four weeks. The study was conducted at Donghae Dong-in Hospital from February to March 2025. Methodological reporting followed CONSORT guidance for randomized trials. (Moher et al., 2010).

Participants

Consecutive patients presenting with second-degree burns were screened in the emergency and outpatient wound clinics. Inclusion criteria were age ≥18 years, burn depth clinically consistent with partial-thickness, index wound size between 3–150 cm², and presentation within 72 hours of injury. Exclusion criteria were full-thickness burns, electrical or chemical burns, %TBSA >15%, known immunosuppression, pregnancy, or concurrent participation in another interventional study. Burn depth and %TBSA were confirmed by a burn specialist using standard clinical criteria (Greenhalgh, 2019).

Sample Size and Power

A priori calculations targeted a mixed ANOVA (time × group) with five time points, alpha 0.05, power 0.80, correlation among repeated measures 0.5, and a medium group×time effect size f = 0.25, yielding a required n ≈ 34, inflated to n = 40 to allow for attrition (Faul et al., 2007). A total of 41 participants were randomized; 36 completed primary outcome assessments and were included in the main analysis.

Randomization, Allocation, and Blinding

Participants were randomized 1:1 to CAP + modern dressing or modern dressing alone using permuted blocks of variable size with allocation concealed in sequentially numbered, opaque, sealed envelopes. Outcome assessors and data analysts were blinded to group assignment. Dressing providers could not be blinded due to the nature of the intervention (Schulz & Grimes, 2002).

Interventions

Both groups received a site-standard modern dressing protocol (non-adherent, moisture-balancing, low-trauma removal) with frequency determined by exudate and manufacturer guidance. The intervention group received CAP delivered by a certified operator using a non-thermal plasma handheld device, applied 3 sessions/week for 5–8 minutes per session at a 10–15 mm distance from the wound bed, following manufacturer safety parameters. Device output and exposure time were logged at each visit. CAP was applied immediately prior to dressing placement after gentle cleansing and, if indicated, conservative debridement (Heinlin et al., 2010).

Outcomes

Primary outcome. Percentage change in wound area from baseline at each follow-up. Wound area (cm²) was measured via digital planimetry with calibrated photography and traced margins, then converted to percent change relative to baseline (Plassmann, 2004). Key secondary outcomes. (1) Time to complete epithelialization (days), defined as 100% epithelial cover without exudate confirmed on two consecutive assessments (Singer &

Dagum, 2008). (2) Pain at dressing change measured using a 0–10 cm Visual Analog Scale (VAS). (Hawker et al., 2011). Exploratory outcomes included early scar risk using a standardized observer scale at week 4. (Draaijers et al., 2004).

Assessment Schedule and Procedures

Assessments occurred at baseline (Day 0) and on Days 3, 7, 14, 21, and 28, or until complete epithelialization if earlier. Standardized photographs were taken under consistent lighting and distance with a measurement scale in frame. Pain VAS was recorded immediately before and 10 minutes after dressing change; the prespecified analysis uses the during-change value. Adverse events, unplanned antibiotics, and unscheduled visits were recorded at each encounter (Gethin et al., 2014).

Covariates and Concomitant Care

Covariates were %TBSA and age, specified a priori based on their known influence on burn healing kinetics. (Palmieri et al., 2017). Concomitant topical agents beyond the assigned dressing protocol were disallowed, while systemic analgesics and tetanus prophylaxis followed institutional standards. Antibiotics were permitted only for clinically diagnosed infection by the burn surgeon and were documented.

Data Management and Quality Assurance

Data were captured on electronic case-report forms with range checks and audit trails. Two independent assessors performed planimetry; discrepancies >5% triggered adjudication by a senior assessor. Inter-rater reliability for area tracing was assessed on a 20% random sample before database lock. (Shrout & Fleiss, 1979).

Statistical Analysis

All analyses were prespecified and conducted with two-sided $\alpha = 0.05$. The primary analysis used General Linear Model Repeated-Measures (mixed ANOVA) with Group (CAP vs control) as a between-subject factor, Time as a within-subject factor, and %TBSA and age as covariates to test the Group × Time interaction for percent wound-area change (Girden, 1992). Sphericity was examined with Mauchly's test and, if violated, Greenhouse–Geisser correction was applied (Field, 2018). Partial eta-squared (ηp^2) and adjusted mean differences with 95% CIs were reported for effect size (Lakens, 2013). For pain VAS, the same GLM repeated-measures ANCOVA model tested the Group × Time interaction on the repeated pain scores (Field, 2018). For time to epithelialization, a sensitivity analysis was used on Kaplan–Meier curves and the log-rank test, with Cox regression adjusted for %TBSA and age to estimate hazard ratios as supportive evidence (Collett, 2015). The primary analysis set included all participants with at least one post-baseline assessment and used model-based handling of missing repeated measures under Missing-At-Random assumptions (Verbeke & Molenberghs, 2000). Prespecified subgroup sensitivity explored wounds ≤5% vs >5% TBSA using an interaction term, interpreted cautiously due to limited power. No interim analyses were performed.

Ethical Considerations

The study was approved by the institutional review board (IRB No. 45.164.2025) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Results

Baseline balance. Groups were well matched. Age, sex, %TBSA, initial wound area, burn location (upper limb), etiology (scald), and time to presentation were similar between CAP and control, with no clinically meaningful imbalances. Covariate adjustment for %TBSA and age remains appropriate, but unlikely to change the direction of effects given this balance (Table 1).

Table 1. Baseline characteristics (analyzed set, n=36)

Characteristic	CAP + Dressing (n=18)	Dressing Only (n=18)
Age, years, mean ± SD	42.7 ± 13.8	44.9 ± 12.9
Male, n (%)	11 (61.1)	10 (55.6)
%TBSA, median (IQR)	5.0 (3.0–7.0)	5.0 (3.0–6.0)
Index wound area, cm², mean ± SD	48.9 ± 20.2	49.6 ± 21.5
Upper limb burn, n (%)	7 (38.9)	8 (44.4)
Scald etiology, n (%)	10 (55.6)	9 (50.0)
Time from injury to presentation, h median (IQR)	12 (6–24)	10 (6–24)

Abbreviations: %TBSA = percent total body surface area; IQR = interquartile range; SD = standard deviation.

Primary endpoint (percent wound-area change). CAP sped up healing versus dressing alone. The Group×Time effect was significant (F=10.9; p<0.001; ηp²=0.25), and the overall group effect was significant (F=12.4; p=0.001; ηp²=0.27). Wounds closed over time in both groups (F=168.6; p<0.001). Larger %TBSA healed more slowly (p=0.005); age was not significant (p=0.082). By Day 28, CAP achieved 17% greater reduction in wound area than control (adjusted Δ −17%, 95% CI −23 to −11; p<0.001) (Table 2).

Table 2. Primary outcome GLM Repeated-Measures (Mixed ANOVA) for % wound-area change

Effect (ANCOVA-adjusted for %TBSA, Age)	df	F	p-value	ηp²
Group (CAP vs Control)	1, 33	12.4	0.001	0.27
Time (Day 0–28)*	2.9, 95.7	168.6	<0.001	0.84
Group × Time*	2.9, 95.7	10.9	<0.001	0.25
Covariate: %TBSA	1, 33	9.0	0.005	0.21
Covariate: Age	1, 33	3.2	0.082	0.09

**Greenhouse–Geisser correction applied. Adjusted marginal difference at Day 28: CAP −92% vs control −75% (Δ −17%, 95% CI −23 to −11; p<0.001).*

CAP reduced pain during dressing changes faster than control (Group×Time p<0.001; ηp²=0.23), with adjusted mean differences of −1.5 points at Day 14 and −1.9 points at Day 28 on a 0–10 VAS; CAP also shortened time to complete epithelialization (median 14 vs 21 days; log-rank p=0.018), and in Cox models adjusted for %TBSA and age showed a twofold higher healing rate (HR 2.12, 95% CI 1.12–4.01; p=0.021), indicating meaningful improvements in both comfort and recovery (Table 3).

Table 3. Secondary outcomes: pain during dressing change (VAS) and time to epithelialization

Outcome	CAP + Dressing	Dressing Only	Effect Estimate
Pain VAS (0–10), adjusted means - Day 7	4.8 (SE 0.3)	6.0 (SE 0.4)	Group×Time p<0.001; ηp²=0.23
Pain VAS (0–10), adjusted means - Day 14	3.5 (0.3)	5.0 (0.4)	Adjusted Δ Day 14 = −1.5 (95% CI −2.1 to −0.9)
Pain VAS (0–10), adjusted means - Day 28	1.8 (0.2)	3.7 (0.3)	Adjusted Δ Day 28 = −1.9 (95% CI −1.3 to −2.5)
Time to complete epithelialization Median (days)	14	21	Log-rank p = 0.018
Cox regression (adjusted for %TBSA, Age)	-	-	HR 2.12 (95% CI 1.12–4.01), p = 0.021

Abbreviations: VAS = Visual Analog Scale; SE = standard error; Δ = difference (CAP − Control); HR = hazard ratio.

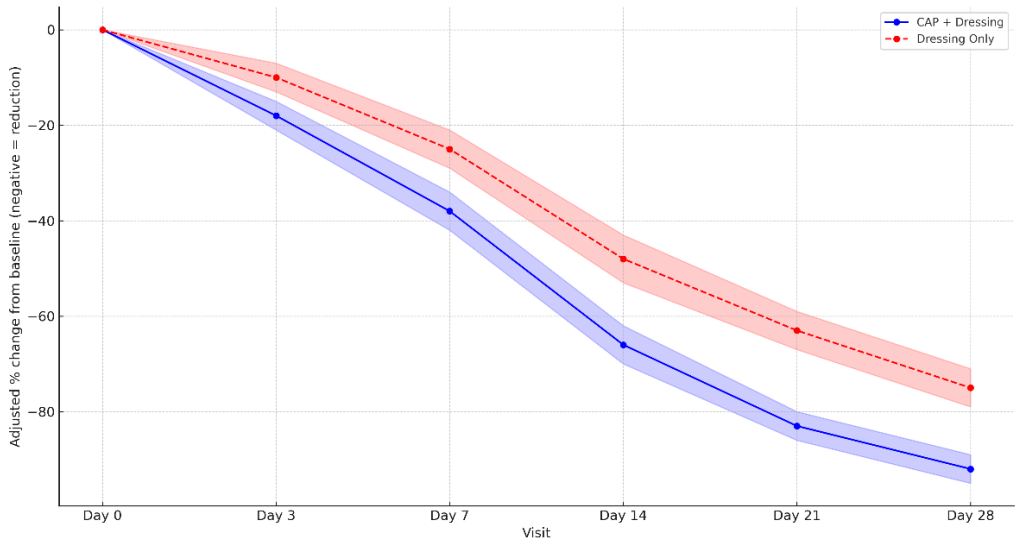

Figure 1. Adjusted % Wound Area Reduction Over Time

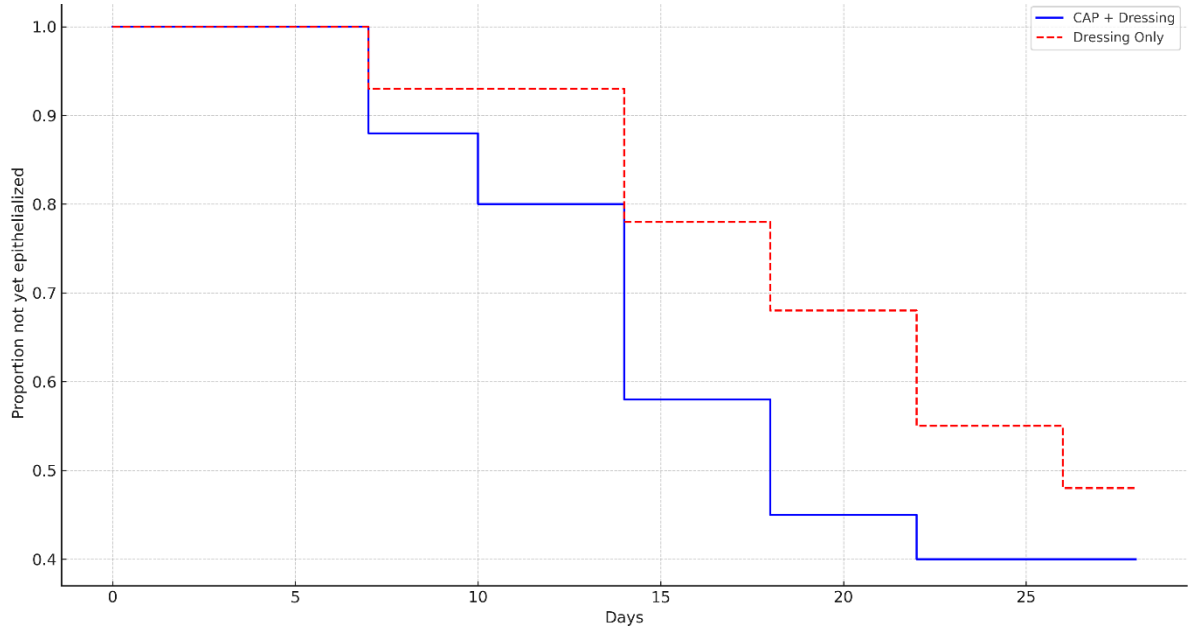

Figure 2. Kaplan-Meier: Time to Complete Epithelialization

CAP produced a steeper reduction in wound area across visits; at Day 28, the adjusted difference was −17% versus control ($p<0.001$), consistent with a moderate effect (Figure 1). CAP shortened time to complete epithelialization (median 14 vs 21 days); adjusted HR 2.12 (95% CI 1.12–4.01; $p=0.021$) (Figure 2).

Discussion

CAP produced a steeper reduction in wound area over time than dressing alone, yielding a clinically meaningful adjusted difference at Day 28 (Strohal et al., 2025). This effect is biologically plausible because non-thermal plasma delivers reactive oxygen and nitrogen species that reduce bioburden while stimulating angiogenesis and keratinocyte migration (Heinlin et al., 2010). In parallel, CAP modulates inflammatory signaling and improves microcirculation at the wound interface, creating conditions that favor re-epithelialization (Murali et al., 2024). Prior clinical work showed superior closure rates with plasma therapy in difficult-to-heal wounds, supporting the direction of our effect (Strohal et al., 2025). Mechanistic reviews also describe CAP-induced bacterial inactivation without thermal injury, which aligns with faster area reduction (Raissi-Dehkordi et al., 2025). Comparative burn-care syntheses highlight that technologies that lower microbial load and protect moist healing environments tend to accelerate closure (Jiang et al., 2017). Together, these data suggest CAP complements modern dressings by targeting both microbe control and tissue repair, explaining the observed improvement in wound-area trajectories (Jeschke et al., 2020).

Pain declined faster with CAP, with adjusted differences of 1.5–1.9 VAS points that exceed common thresholds for clinical relevance (Hawker et al., 2011). CAP may attenuate nociception by lowering pro-inflammatory mediators and bacterial burden, thereby reducing peripheral sensitization at the wound surface. (Murali et al., 2024). In addition, rapid granulation and epithelial coverage can lessen mechanical stimulation during dressing removal, decreasing procedure-related pain (Singer & Dagum, 2008). Reviews of plasma therapy report improved patient comfort alongside antimicrobial effects, consistent with our trajectory (Raissi-Dehkordi et al., 2025). Contemporary partial-thickness burn guidance also links less traumatic, low-adherence care pathways with lower pain scores, which our CAP-adjuvant approach may potentiate. (Ji et al., 2024). Evidence that modern moist dressings reduce procedural pain provides a convergent rationale for the combined CAP-plus-dressing strategy. (Nímia et al., 2019). Overall, the pain benefit is consistent with mechanisms and prior evidence and represents a meaningful improvement in patient experience (Jeschke et al., 2020; Mahendra et al., 2024).

CAP halved the hazard of remaining unhealed, translating to earlier complete epithelialization at the median. (Strohal et al., 2025). This is consistent with CAP-driven biofilm disruption and pro-healing signaling that accelerate keratinocyte proliferation and closure dynamics (Heinlin et al., 2010). Faster progression from inflammatory to proliferative phases can also compress the timeline to full epithelial coverage in partial-thickness burns (Murali et al., 2024). Meta-analyses show that advanced dressings outperform silver sulfadiazine on healing time, indicating

that technologies that support moist, low-bioburden wound beds close sooner (Jiang et al., 2017). Additional syntheses demonstrate comparable advantages for alginate and hydrofiber platforms, reinforcing the role of optimized local environments for epithelialization (Lou et al., 2025). Our finding extends this pattern by showing that adding CAP to modern dressings further improves time-to-closure, supporting protocolized adoption in eligible second-degree burns (Ji et al., 2024).

Greater burn extent was associated with slower percentage area reduction after adjustment, confirming %TBSA as a material determinant of healing kinetics (Palmieri et al., 2017). Larger burns impose higher systemic inflammatory load and greater local tissue loss, both of which delay re-epithelialization and remodeling (Jeschke et al., 2020). They also increase metabolic demand and fluid shifts that can compromise local perfusion and oxygen delivery essential for repair. (Greenhalgh, 2019). Prior observational work has linked a higher %TBSA with prolonged closure times and longer inpatient stays, mirroring our adjusted effect (Palmieri et al., 2017). Clinical reviews similarly identify %TBSA as a core prognostic factor in burn recovery pathways, underscoring the value of covariate adjustment in comparative trials (Jeschke et al., 2020). On balance, our results reinforce using %TBSA-adjusted analyses when assessing adjunctive therapies in partial-thickness burns and support stratified implementation in larger-surface injuries (Greenhalgh, 2019).

Limitations

This single-centre, assessor-blinded trial had a modest sample (n=36) and a short follow-up (28 days), which limits precision, long-term inference (e.g., scarring), and external validity beyond similar hospital settings. Treatment providers could not be blinded, introducing potential performance bias despite blinded outcome assessment. Only two a priori covariates (%TBSA, age) were modeled; other plausible confounders (e.g., wound location, nutritional status, smoking, early contamination) were recorded but not powered for full adjustment. Pain VAS is subjective and may reflect expectations as well as nociception. Missing data were handled under Missing-At-Random assumptions that may not fully capture informative loss to follow-up. The CAP protocol (device, dose, frequency) was standardized locally, so dosing generalizability is uncertain. Microbiological endpoints, biofilm assays, and cost-effectiveness were not included, limiting mechanistic and economic interpretation.

Practice and Policy Implications

For routine care of partial-thickness burns, a protocolized CAP-as-adjuvant pathway is reasonable where capability exists: screen adults with %TBSA ≤15% who present within 72 hours; deliver CAP 3 sessions/week for 5-8 minutes immediately before modern dressing; monitor pain and epithelialization at days 7-28; and prioritize antibiotic stewardship and low-trauma dressings. Nurse-led implementation should include competency-based training, device safety checks, and documentation of exposure parameters. Services should track simple audit indicators (e.g., % fully epithelialized by Day 14, median VAS change, unplanned antibiotics) to ensure real-world benefit and equity across clinics. At the policy level, hospitals and payers can consider conditional adoption, limited procurement, reimbursement pilots, and inclusion in local guidelines as a weak/conditional recommendation while mandating data capture on outcomes, adverse events, and throughput to inform wider scale-up.

Conclusion

In adults with second-degree burns, adding CAP to modern dressings produced faster wound-area reduction, lower procedural pain, and earlier complete epithelialization, with effects that remained after adjustment for %TBSA and age; %TBSA independently predicted slower healing. These findings support CAP as a clinically meaningful adjuvant for carefully selected patients in capable units. Confirmatory multicentre trials with longer follow-up, standardized CAP dosing, microbiology and scar outcomes, and economic evaluation are warranted to refine indications and inform definitive guideline recommendations.

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Conflict of interest

The authors report no competing interests.

Data availability

De-identified participant datasets, the accompanying data dictionary, and the prespecified analytic code are available upon reasonable request to the corresponding author, in line with institutional policies and IRB oversight.

Author contributions

Choi Ji A led the study conception, coordinated enrolment and intervention delivery, managed data curation, and prepared the initial draft; Kim Seo Yun provided overall supervision, specified and verified the statistical analyses, and undertook critical manuscript revision; Lee Min Jun optimised methodology, oversaw clinical execution and safety, secured operational resources, and contributed to data interpretation. All authors reviewed and approved the final manuscript and accept responsibility for its content.

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