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Jet Cold Plasma at Atmospheric Air Pressure for Venous Ulcers: A Randomized Clinical Trial

Angel Henares, MD*
Sonia Villajos, BSN†
Antonio Tejera, PhD†
Lucía Gutiérrez, PhD†
Iñigo Arroyo, MD*
Naroa Moreno, MD*
Ignacio Leal, MD*
Loreto Rubio, BSN*
Javier Buendía, MD‡
José Lasso, MD, PhD§
Ana Megía-Macías, PhD¶‖
Osvaldo-Daniel Cortázar, PhD‖
Bernardo Hontanilla, MD, PhD*

Background: This prospective, randomized, controlled, open-label, multicenter clinical trial evaluated the efficacy and safety of air-based cold atmospheric plasma jet (CAPJ) therapy for chronic venous leg ulcers (VLUs) compared with standard of care (SOC).

Methods: Sixty adult patients with nonhealing VLUs were randomized to receive either CAPJ therapy twice weekly for 10 weeks or SOC. The primary outcome was the percentage reduction in wound area at weeks 4, 9, and 17. Secondary outcomes included granulation tissue formation, microbial burden (qualitative and quantitative), pain (visual analog scale), aesthetic satisfaction, and adverse events. Analyses were performed on an intention-to-treat basis.

Results: Both groups demonstrated progressive reductions in wound area over time. Although the CAPJ group exhibited a greater mean reduction (−72.9% versus −56.7% at week 17), the difference was not statistically significant ($P = 0.30$). Complete healing was achieved in 42.9% of CAPJ patients compared with 30.4% in the SOC group ($P = 0.361$). CAPJ produced significant immediate decreases in microbial burden at weeks 0 and 4 ($P < 0.05$). Pain scores improved similarly in both groups, and aesthetic satisfaction was high without significant intergroup differences. No serious adverse events were attributed to the device; transient pain-related sensations were the most frequent treatment-related effects.

Conclusions: Although not statistically superior to SOC, air CAPJ therapy resulted in clinically meaningful wound area reduction, rapid antimicrobial effects, and high patient acceptability without increased adverse events. These findings support further investigation of CAPJ as a safe, noninvasive therapy for chronic VLU management. *(Plast Reconstr Surg Glob Open 2026;14:e7553; doi: 10.1097/GOX.0000000000007553; Published online 18 March 2026.)*

*From the *Department of Plastic and Reconstructive Surgery, Clínica Universidad de Navarra, Pamplona, Spain; †Hospital Universitario La Mancha Centro, Unidad de Heridas, Ciudad Real, Spain; ‡Department of Plastic and Reconstructive Surgery, Hospital Clínico San Carlos, Madrid, Spain; §Department of Plastic and Reconstructive Surgery, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ¶Mechanical Engineering Department, Superior Industrial School of Engineering, Comillas Pontifical University, Madrid, Spain; and ‖Institute of Technological Research, Comillas Pontifical University, Madrid, Spain.*

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INTRODUCTION

Venous leg ulcers (VLUs) are a prevalent clinical condition that places a substantial burden on healthcare systems. They account for 1%–2% of healthcare budgets in Europe[1] and approximately $15 billion annually in the United States.[2] The incidence ranges from 0.3 to 1 per 1000 individuals per year, rising to 3 per 1000 in those aged 65 years or older.[3,4] VLUs are characterized by a high recurrence rate (71%), healing times exceeding 1 year in half of the cases, and frequent infections. Therefore, VLUs significantly impair patients' quality of life and highlight the need for innovative treatment approaches.[5,6]

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

Cold atmospheric plasma (CAP) has emerged as a promising therapy for chronic wounds.[7] CAP generates electric fields and a mixture of reactive oxygen and nitrogen species that enhance microcirculation, exert antimicrobial effects, and support key regenerative processes such as angiogenesis, cell proliferation, and modulation of inflammation.[8–15] Unlike argon or helium-based CAP jets (CAPJs), which dominate the literature and require specialized gases and costly equipment,[6,7,16–19] air CAPJs use ambient air, lowering costs and simplifying use.[20] For these reasons, air CAPJs represent a more accessible and potentially effective alternative in clinical practice.

This study introduced a novel device designed to deliver air CAPJ efficiently and sustainably. It is easily transportable, requires no consumables, and enables a more precise and reproducible treatment of the ulcer bed, addressing key limitations of existing CAPJ systems.[21] Our primary hypothesis was that this new air CAPJ device would reduce the surface area of venous ulcers and decrease their bacterial burden. This hypothesis was informed by observations from previous compassionate-use cases in which large nonvascular ulcers achieved rapid closure with this treatment.

Objectives

The primary objective was to determine the efficacy of treatment using air CAPJ for chronic VLUs, focusing on its ability to promote healing and reduce wound size over the treatment period. Secondary objectives included assessing patient satisfaction and safety.

METHODS

Study Design

This clinical trial was designed as a prospective, randomized, controlled, open-label, multicenter study aimed to evaluate the efficacy and safety of air CAPJ compared with standard of care (SOC) in patients with chronic VLUs. Each participant was followed up for 18 weeks, including a 10-week treatment phase and an 8-week follow-up period. The study procedures were performed, and all effectiveness and safety measurements were assessed according to the diagram presented in Supplemental Digital Content 1. (**See figure, Supplemental Digital Content 1**, which displays the timeline of the clinical trial showing recruitment, treatment procedures, and scheduled assessments across all study visits, **https://links.lww.com/PRSGO/E712**.)

Population

Eligible patients were adults (>18 y) with at least 1 VLU greater than 1 cm^2, nonhealing for more than 3 weeks, without a surgical indication for grafting (absence of adequate granulation tissue), and who provided signed informed consent. These criteria were applied across all participating centers. Exclusion criteria included uncontrolled diabetes (HbA1c >8%), allergy to silver or materials used in wound care, ongoing VAC therapy, use of topical antibiotics within 48 hours, critical limb ischemia (ankle-brachial index < 0.5 or transcutaneous oxygen pressure < 15 mm Hg), use of corticosteroids or immunosuppressants in the previous 14 days, chronic or active skin disorders impairing healing, pregnancy or breastfeeding, advanced/metastatic cancer, nutritional deficiencies, dementia, radiation-induced wounds, or sepsis.

Takeaways

Question: Can air-based cold atmospheric plasma jet (CAPJ) therapy accelerate healing in chronic venous leg ulcers compared with standard care?

Findings: In this randomized multicenter clinical trial (n = 60), CAPJ applied twice weekly for 10 weeks achieved a greater mean wound area reduction at week 17 (–72.9% versus –56.7%) compared with standard alginate-silver dressings, although the difference was not statistically significant. CAPJ also produced an immediate, marked reduction in bacterial load postapplication. The device was portable, consumable-free, and intuitive. No serious device-related adverse events occurred.

Meaning: Air CAPJ is a safe, well-tolerated, and potentially effective adjunct therapy for venous ulcers, offering rapid antimicrobial effects and encouraging trends in wound healing.

Randomization and Group Assignment

Patients were randomized to the experimental or control group using a block randomization method. Randomization was carried out centrally by a program specifically designed for the trial. Allocation concealment was maintained by sealed, sequentially numbered envelopes.

Intervention and Comparator

The patients in the experimental group were treated with air CAPJ using a portable device designed for localized applications via a jet. This device (PlasmAction Med) belongs to the Spanish company ION BIOTEC S.L. The application was performed directly on the surface of the ulcer with a power of 55% for 60 seconds per cm^2, twice a week for 10 weeks. Subsequently, the ulcer was covered with an absorbent alginate dressing (Melgisorb Ag).[22] At baseline (week 0), mid-treatment (week 4), and at the end of treatment (week 9), wound cultures were obtained before and immediately after plasma application. Patients in the control group received standard treatment, consisting of the application of Melgisorb Ag, replaced twice a week during the same period. Wound cultures were obtained at the aforementioned control points. All patients in both groups received standard compression therapy throughout the study, as they all presented with chronic venous insufficiency.

Outcome Variable and Measures

The primary outcome was the percentage reduction in wound area from baseline to weeks 4, 9, and 17, measured via standardized photography and analyzed with ImageJ2. A more than 10% decrease was considered significant; complete closure was defined as full

epithelialization. Granulation tissue was scored (0–3) by a single trained plastic surgeon based on photographs (0 = none; 1 = partial coverage; 2 = full coverage; 3 = complete closure).

Secondary outcomes included pain (visual analog scale [VAS] 0–10), infection signs (heat, exudate, local temperature), and microbiological status (swabs at baseline, week 4, and week 9). Both qualitative (colony growth described as low, moderate, or high) and quantitative (colony-forming units, CFUs) data were analyzed centrally. Quantitative bacterial load was obtained by swabbing the wound and plating samples onto agar media for viable cell counts (CFUs). Aesthetic satisfaction was measured at week 17 using the aesthetic numeric analog scale completed by the patient. Adverse events (AEs) were monitored throughout and classified according to MDCG 2020-10/1 and EU Regulation 2017/745.

Sample Size and Statistical Analysis

The sample size was based on an expected 40% response rate in the control group versus 80% in the experimental group, with 90% power and a 2-sided alpha of 0.05. Allowing for a 10% dropout rate, the target sample size was 68 patients; however, 60 (30 per group) were ultimately enrolled due to recruitment constraints (Fig. 1). Recruitment spanned 20 months across 4 clinical centers: Clínica Universidad de Navarra, Hospital General Universitario Gregorio Marañón, Hospital General La Mancha Centro, and Hospital Clínico de San Carlos.

Data were analyzed by the intention-to-treat principle. Quantitative variables were summarized as means, SDs, medians, and interquartile ranges; categorical variables, as counts and percentages. Intergroup comparisons used the Pearson χ^2 test or the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous/ordinal variables. Intragroup comparisons used the Wilcoxon signed-rank test. Two-tailed *P* values less than 0.05 were considered significant. Analyses were performed using Stata v18.

RESULTS

Baseline Characteristics

Both control and experimental groups were demographically comparable. Mean age was 69.1 years (SD 14.5 y) and 68.0 years (SD 15.8 y), respectively. Mean weight and height were 93.5 kg (SD 25.8 kg) and 169.9 cm (SD 13.0 cm) in the control group versus 97.0 kg (SD 28.7 kg) and 167.7 cm (SD 12.3 cm) in the experimental group. Men accounted for 70% of the control group and 53.3% of the experimental group; tobacco use was reported in 10% and 16.7%, respectively. No significant differences were found. Similarly, baseline values for primary and secondary outcomes did not differ significantly between groups, confirming their comparability before treatment (Table 1).

Wound Area Reduction

Wound area was assessed as an absolute value and a percentage change at weeks 4, 9, and 17. Both groups showed significant intragroup reductions over time (all $P < 0.01$), with no significant intergroup differences. At baseline, mean wound area was 13.2 cm^2 (SD 18.2 cm^2) in the experimental group and 14.2 cm^2 (SD 18.6 cm^2) in the control group ($P = 0.50$). By week 4, it had decreased to 9.1 cm^2 (SD 14.7 cm^2) and 7.5 cm^2 (SD 11.4 cm^2), respectively ($P = 0.74$), and by week 17 to 4.6 cm^2 (SD 9.6 cm^2)

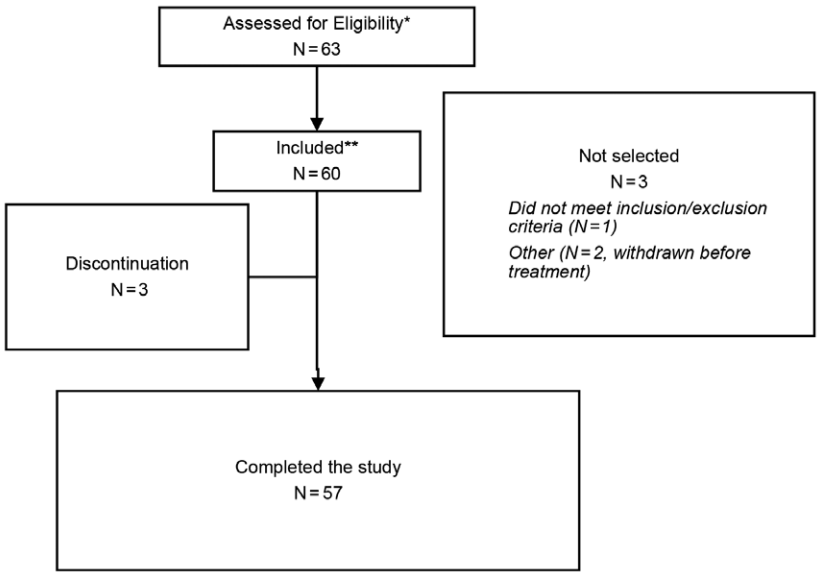

Fig. 1. CONSORT flow diagram showing participant screening, enrollment, allocation, follow-up, and analysis. *Subject having signed a consent form. **Subject having received the investigational device. CONSORT, Consolidated Standards of Reporting Trials.

Table 1. Baseline Clinical Outcomes for Both Groups, Including Wound Surface Area, Granulation Tissue, Microbiological Status (Qualitative and Quantitative), and Pain Scores

	Group	N	Mean	SD	p50	p25	p75	Minimum	Maximum
Area (wound surface)	Control	30.00	13.22	17.34	5.56	3.18	18.22	1.00	63.36
	Experimental	30.00	15.33	19.83	5.13	2.33	21.51	0.98	66.12
	Total	60.00	14.28	18.50	5.40	2.50	18.89	0.98	66.12
Granulation tissue	Control	30.00	0.60	0.50	1.00	0.00	1.00	0.00	1.00
	Experimental	30.00	0.60	0.50	1.00	0.00	1.00	0.00	1.00
	Total	60.00	0.60	0.49	1.00	0.00	1.00	0.00	1.00
Microbiology: qualitative report	Control (pre)	27.00	2.00	0.73	2.00	1.00	3.00	1.00	3.00
	Experimental (pre)	25.00	2.24	0.72	2.00	2.00	3.00	1.00	3.00
	Total (pre)	52.00	2.12	0.73	2.00	2.00	3.00	1.00	3.00
	Experimental (post)	23.00	1.48	0.59	1.00	1.00	2.00	1.00	3.00
Microbiology: quantitative report, CFU	Control (pre)	27.00	3.1×10^6	1.1×10^7	10,010.00	150.00	1.0×10^5	0.00	4.3×10^7
	Experimental (pre)	27.00	1.0×10^6	4.2×10^6	30,000.00	10,000.00	2.9×10^5	0.00	2.2×10^7
	Total (pre)	54.00	2.1×10^6	8.3×10^6	20,000.00	1200.00	1.6×10^5	0.00	4.3×10^7
	Experimental (post)	26.00	5.8×10^5	2.9×10^6	300.00	0.00	10,000.00	0.00	1.5×10^7
PAIN (VAS)	Control	30.00	3.43	3.77	2.00	0.00	7.00	0.00	10.00
	Experimental	28.00	3.39	3.47	2.00	0.00	6.00	0.00	10.00
	Total	58.00	3.41	3.59	2.00	0.00	6.00	0.00	10.00

Data are presented as mean, SD, median, interquartile range, minimum, and maximum values.

and 6.7 cm^2 (SD 14.5 cm^2) ($P = 0.50$) (Table 2). Percentage reduction, as the primary outcome, was greater in the experimental group, but differences were not statistically significant (Table 3): –41.8% versus –36.1% at week 4 ($P = 0.98$), –42.5% versus –42.9% at week 9 ($P = 0.75$), and –72.9% versus –56.7% at week 17 ($P = 0.30$). Complete wound closure at week 17 occurred in 12 of 28 (42.9%) experimental and 7 of 23 (30.4%) control patients ($P = 0.361$) (Table 4), due to loss to follow-up.

Although not statistically significant, a higher proportion of patients in the experimental group achieved more than 10% wound area reduction at all time points: 88.9% versus 76.0% at week 4 ($P = 0.284$), 90.9% versus 81.0% at week 9 ($P = 0.412$), and 89.3% versus 78.3% at week 17 ($P = 0.442$). For illustrative examples of VLU evolution under air CAPJ treatment, see Figures 2 and 3.

Granulation Tissue Formation

Granulation was measured on a 0–3 scale, with higher scores indicating better healing. Baseline values were similar (control: 0.62 ± 0.50; experimental: 0.64 ± 0.49; $P = 0.8361$). Both groups improved over time with no significant differences at weeks 4 ($P = 0.4395$), 9 ($P = 0.1327$), or 17 ($P = 0.8298$) (Fig. 4).

Intragroup analysis showed significant improvement at all time points. Control scores increased from 0.62 to 1.35 (week 4), 1.64 (week 9), and 1.92 (week 17); experimental scores rose from 0.64 to 1.50, 1.93, and 1.96, respectively (all $P < 0.0001$). Despite these gains, no significant differences emerged between groups. Clinicians also noted a consistent "flash effect"—a transient reddening of the wound bed immediately after air CAPJ application—likely due to acute vasodilation (Fig. 5).

Qualitative Microbial Load Assessment

Microbial burden was first evaluated using a qualitative 3-point scale (1 = mild, 2 = moderate, 3 = high). Three comparisons were performed (Fig. 6).

Intergroup Comparison Before Plasma Application

No statistically significant differences were found at baseline or during follow-up for the preapplication microbial scores (week 0: 2.15 versus 2.22, $P = 0.7095$; week 4: 2.23 versus 2.35, $P = 0.6308$; week 9: 2.38 versus 2.46, $P = 0.7165$).

Intergroup Comparison After Plasma Application

The experimental group had significantly lower scores in week 0 (1.48 versus 2.15, $P = 0.0112$) and week 4 (1.41 versus 2.23, $P = 0.0010$); no difference was found at week 9 (2.00 versus 2.38, $P = 0.2103$).

Intragroup Comparison in the Experimental Group

CAP application significantly reduced microbial burden at all time points: week 0 (2.17 → 1.48, $P = 0.0010$), week 4 (2.05 → 1.41, $P = 0.0010$), and week 9 (2.46 → 2.00, $P = 0.0463$).

Quantitative Microbial Load Assessment

Mean quantitative bacterial loads (CFU ± SD) are presented in Figure 7. At baseline, there were no significant differences between the control and experimental groups (week 0: $3.8 \times 10^6 \pm 1.2 \times 10^7$ versus $1.1 \times 10^6 \pm 4.4 \times 10^6$, $P = 0.352$; week 4: $6.0 \times 10^6 \pm 1.8 \times 10^7$ versus $2.5 \times 10^6 \pm 6.8 \times 10^6$, $P = 0.216$; week 9: $1.2 \times 10^6 \pm 3.3 \times 10^6$ versus $4.7 \times 10^5 \pm 1.2 \times 10^6$, $P = 0.879$).

Following plasma application, the experimental group exhibited significantly lower CFU counts than the control group at week 0 ($5.8 \times 10^5 \pm 2.9 \times 10^6$ versus $3.8 \times 10^6 \pm 1.2 \times 10^7$, $P = 0.016$) and week 4 ($1.8 \times 10^5 \pm 9.0 \times 10^5$ versus $6.0 \times 10^6 \pm 1.8 \times 10^7$, $P = 0.014$), with no difference at week 9 ($4.9 \times 10^5 \pm 1.6 \times 10^6$ versus $1.2 \times 10^6 \pm 3.3 \times 10^6$, $P = 0.736$).

Within the experimental group, CAP produced significant reductions in bacterial load in week 0 ($1.1 \times 10^6 \rightarrow 5.8 \times 10^5$, $P = 0.031$) and week 4 ($2.5 \times 10^6 \rightarrow 1.8 \times 10^5$,

Table 2. Evolution of Wound Surface Area (cm²) for Control and Experimental Groups at Weeks 0, 4, 9, and 17

Group	N	Mean	SD	p50	p25	p75	Minimum	Maximum
Week 0								
Control	25.00	14.16	18.60	6.07	3.18	18.22	1.02	63.36
Experimental	27.00	13.23	18.23	4.12	1.56	16.23	0.98	62.67
Total	52.00	13.67	18.23	4.79	2.06	17.48	0.98	63.36
$P = 0.5038$; $P(e) = 0.5099$								
Week 4								
Control	25.00	7.48	11.36	2.19	1.24	9.34	0.00	50.42
Experimental	27.00	9.10	14.67	2.10	0.64	8.21	0.07	48.70
Total	52.00	8.32	13.08	2.11	1.20	9.25	0.00	50.42
$P = 0.7416$; $P(e) = 0.7473$								
Week 0								
Control	21.00	13.77	17.76	6.08	3.18	18.22	1.02	63.36
Experimental	22.00	16.09	19.23	7.03	2.86	21.51	0.98	62.67
Total	43.00	14.96	18.34	6.08	2.86	19.57	0.98	63.36
$P = 0.8650$; $P(e) = 0.8758$								
Week 9								
Control	21.00	8.79	18.24	3.00	0.68	7.99	0.13	83.47
Experimental	22.00	8.10	12.02	3.17	0.55	12.44	0.04	43.68
Total	43.00	8.44	15.19	3.00	0.67	12.44	0.04	83.47
$P = 0.9129$; $P(e) = 0.9186$								
Week 0								
Control	23.00	12.12	17.33	5.06	1.70	16.75	1.00	63.36
Experimental	28.00	15.56	20.31	5.13	2.50	18.87	1.01	66.12
Total	51.00	14.01	18.92	5.06	1.80	16.75	1.00	66.12
$P = 0.6771$; $P(e) = 0.6830$								
Week 17								
Control	23.00	6.73	14.52	0.76	0.00	4.55	0.00	65.19
Experimental	28.00	4.59	9.61	0.84	0.00	3.03	0.00	37.04
Total	51.00	5.55	11.99	0.76	0.00	3.87	0.00	65.19
$P = 0.5025$; $P(e) = 0.5082$								

Descriptive statistics (mean, SD, median, interquartile range, minimum, maximum) and Brunner–Munzel *P* values, including permuted $P(e)$ values, are provided for each time point.

Table 3. Percentage Change in Wound Surface Area From Baseline for Control and Experimental Groups at Follow-up Visits (Weeks 4, 9, and 17)

	N	Mean	SD	p50	p25	p75	Minimum	Maximum
Week 4								
Control	25.00	−36.09	44.49	−52.95	−64.86	−20.42	−100.00	64.04
Experimental	27.00	−41.78	32.48	−37.84	−70.19	−15.51	−94.80	32.65
Total	52.00	−39.04	38.44	−47.94	−65.16	−17.96	−100.00	64.04
$P = 0.9781$; $P(e) = 0.9855$								
Week 9								
Control	21.00	−42.91	49.12	−59.68	−72.70	−23.68	−96.27	108.33
Experimental	22.00	−42.54	70.60	−58.13	−81.34	−21.25	−98.79	241.84
Total	43.00	−42.72	60.34	−59.27	−80.06	−21.25	−98.79	241.84
$P = 0.7521$; $P(e) = 0.7637$								
Week 17								
Control	23.00	−56.68	65.01	−78.83	−100.00	−42.91	−100.00	177.27
Experimental	28.00	−72.93	40.21	−92.10	−100.00	−64.02	−100.00	58.42
Total	51.00	−65.60	52.91	−89.02	−100.00	−56.78	−100.00	177.27
$P = 0.3029$; $P(e) = 0.3100$								

Descriptive statistics (mean, SD, median, interquartile range, minimum, maximum) and Brunner–Munzel *P* values, including permuted $P(e)$ values, are provided for each time point.

$P = 0.010$), but not in week 9 ($4.7 \times 10^5 \rightarrow 4.9 \times 10^5$, $P = 0.209$), indicating a transient antimicrobial effect. The control group showed no significant within-group changes over time (all $P > 0.4$).

Pain Evaluation

Pain was assessed using the VAS at baseline (week 0) and weeks 4 and 9. VAS scores decreased in both groups over time. In the control group, mean scores decreased

from 2.92 (SD 3.68) to 1.52 in week 4 ($P = 0.0350$) and 1.00 at week 9 ($P = 0.0132$). In the experimental group, scores fell from 3.44 (SD 3.52) to 2.22 at week 4 ($P = 0.1051$) and to 2.05 at week 9 ($P = 0.0382$). Only the reduction at week 9 reached significance.

No significant differences were found between groups at week 4 ($P = 0.1988$) or week 9 ($P = 0.2618$) (Table 5), indicating similar pain trends in both groups and suggesting that CAPJ was equally well tolerated. These results support the safety and acceptability of the experimental therapy, with no evidence of increased discomfort compared with SOC (Table 6).

Table 4. Complete Wound Healing Rates for Control and Experimental Groups at the End of Follow-up

	Group		
	Control	Experiment	Total
No healing, n	16	16	32
%	69.57	57.14	62.75
Healing (100%), n	7	12	19
%	30.43	42.86	37.25
Total, n	23	28	51
%	100.00	100.00	100.00

Absolute counts and percentages are presented for patients achieving complete healing (100%) and those without complete healing, along with the corresponding *P* value.
$P = 0.361$.

Aesthetic Satisfaction

Aesthetic outcomes were evaluated using the aesthetic numeric analog scale questionnaire at the final follow-up visit (week 17). The control group (n = 22) reported a mean score of 7.95 (SD = 2.98), with a median of 9.00 and an interquartile range of 7.00–10.00. The experimental group (n = 28) had a mean score of 7.32 (SD = 3.04), a median of 8.00, and an interquartile range of 6.00–9.50. Both groups presented the full possible score range, with minimum values of 0.00 and maximum values of 10.00. No statistically significant differences were found ($P = 0.2021$; $P(e) = 0.2060$).

Adverse Events

A total of 102 AEs were reported during the study. Five were classified as serious—4 in the control group and 1

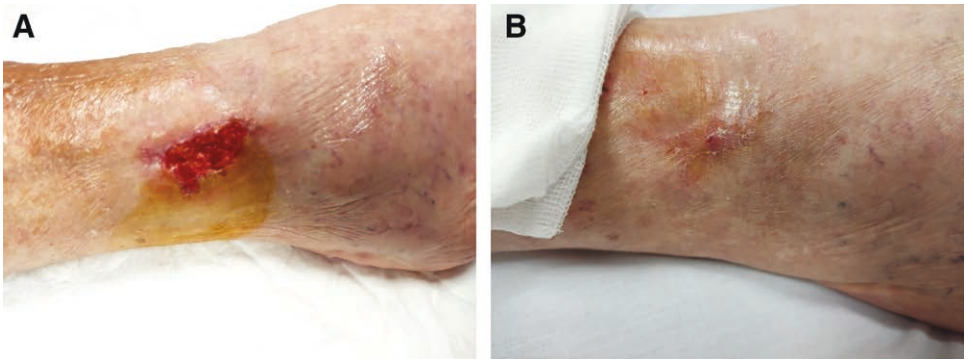

Fig. 2. Clinical photograph. A, Clinical photograph of a VLU in a patient from the experimental group at baseline. B, Complete epithelialization of a VLU after air CAPJ treatment of the same patient after 4 weeks of treatment.

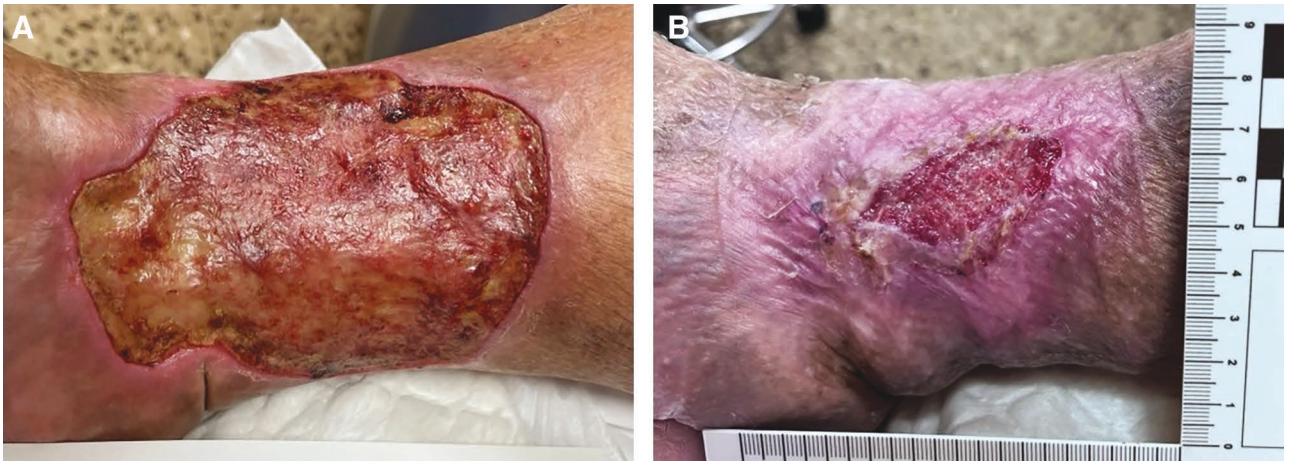

Fig. 3. Refractory VLU before air CAPJ treatment. A, Clinical photograph of a VLC in a patient from the experimental group at baseline. B, Same patient at the end of follow-up.

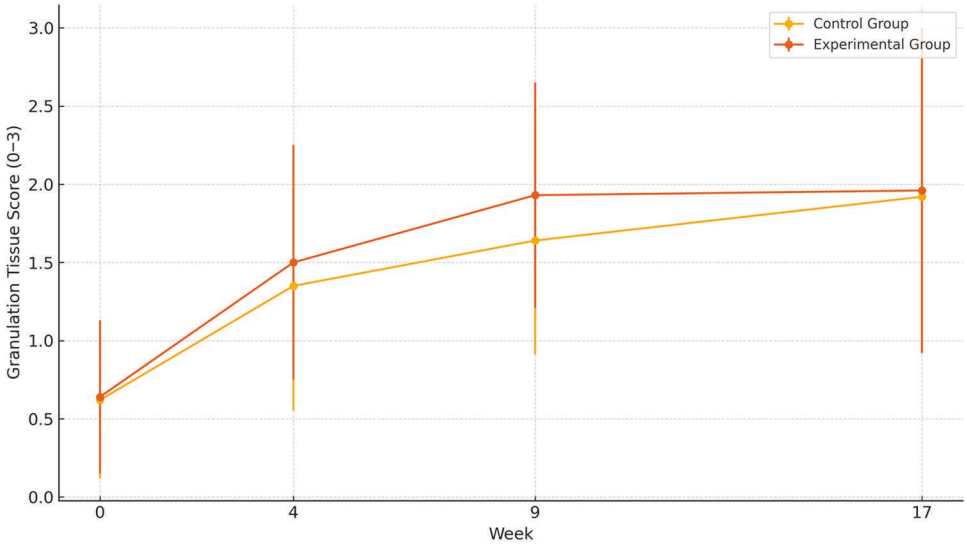

Fig. 4. Mean granulation tissue scores (0–3) for the control and experimental groups at weeks 0, 4, 9, and 17.

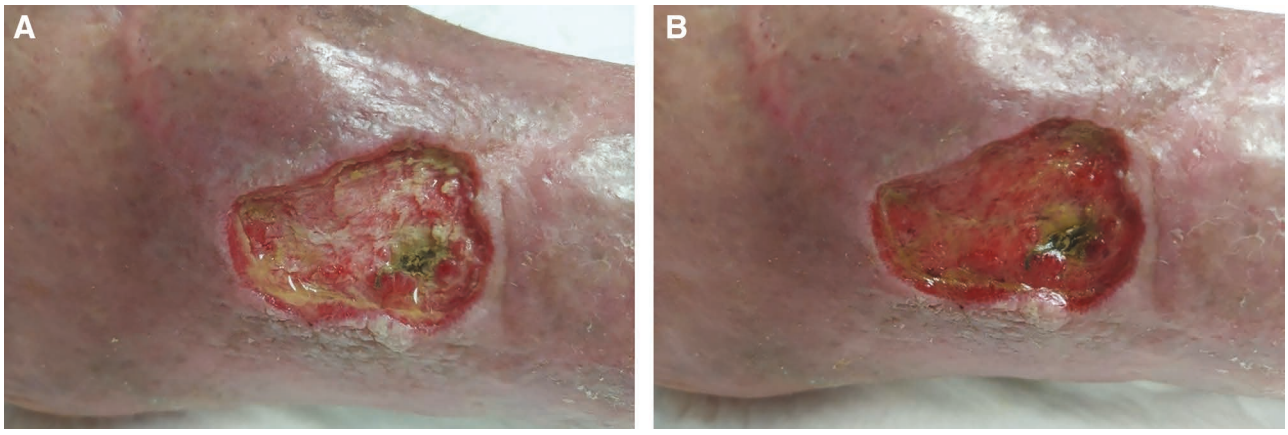

Fig. 5. Clinical photographs. Clinical photographs of a VLU immediately before (A) air and after (B) CAPJ application.

in the experimental group—but none were considered related to the medical device.

Seventeen events were directly related to the treatment, all associated with pain and described by patients as stinging, prickling, or cramping sensations during CAP application. An additional 22 events were deemed likely related and 7 possibly related to the treatment. Most of these events also involved discomfort described as stinging or prickling. This group also included 3 cases of eczema, 1 of erythema, and 2 of wound maceration. The remaining events were classified as unlikely or unrelated to treatment, with 2 rated as having an unknown relationship.

DISCUSSION

The most important finding of this clinical trial is the rapid and statistically significant reduction in bacterial load immediately after CAP treatment. Although the difference in ulcer area reduction between the experimental and control groups did not reach statistical significance, the CAPJ-treated group achieved a clinically meaningful 16.25% greater decrease by the end of the study, surpassing the predefined threshold of 10% improvement.

This aligns with previous small-scale studies reporting reductions of 10%–20% in chronic wound area. For example, Ulrich et al[23] observed a 17% decrease in lower limb ulcers (n = 16) in a small sample. Isbary et al[24] and Stratmann et al[19] both noted approximately 10% improvements, and Brehmer et al[25] described a 20% reduction, although without statistical significance in a cohort of only 14 patients. Other studies have reported statistically significant outcomes in different wound types, including trials by Chuangsuwanich et al[16] on pressure ulcers, Mirpour et al[26] on diabetic foot ulcers (combining CAP + SOC), Heinlin et al[18] on skin grafts, and Rached et al[27] on chronic wounds in general.

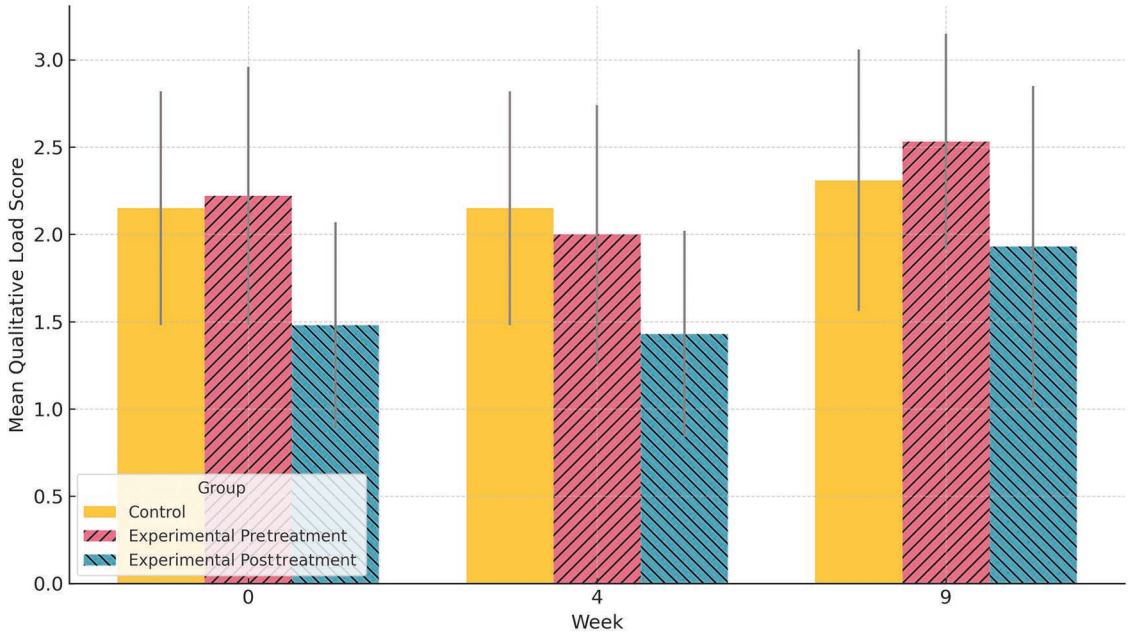

Fig. 6. Mean qualitative microbial load scores for the control group and for pre- and posttreatment measurements in the experimental group at weeks 0, 4, and 9.

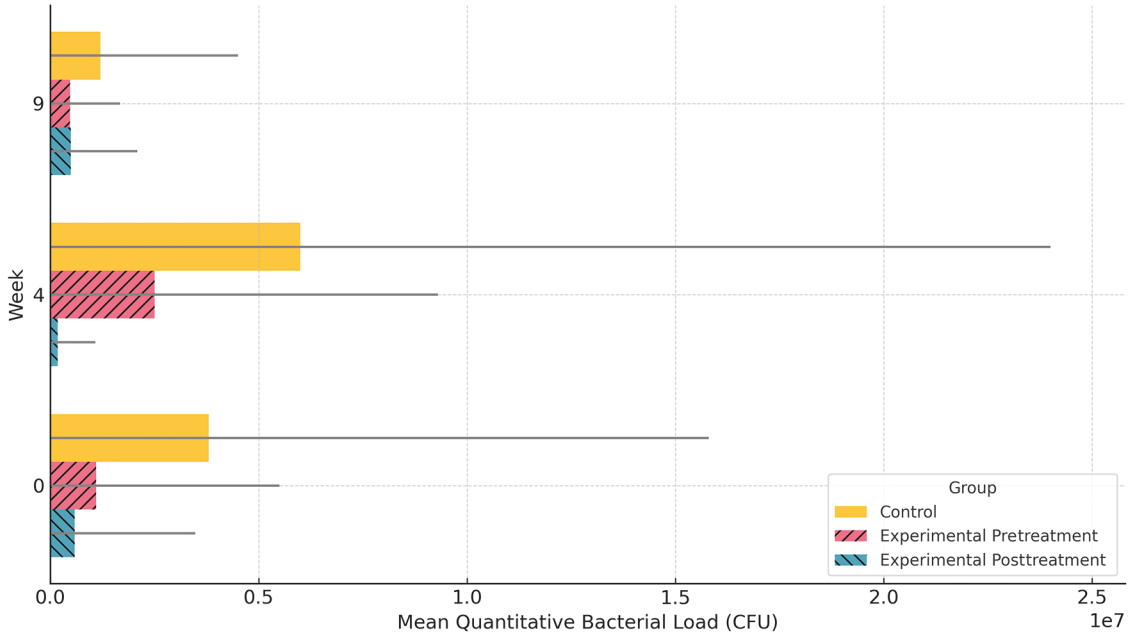

Fig. 7. Mean quantitative bacterial load (CFU) for the control group and for pre- and posttreatment measurements in the experimental group at weeks 0, 4, and 9.

Granulation Tissue Formation and the "Flash Effect"

Although long-term granulation scores were comparable between groups, investigators consistently observed an immediate, intense redness of the wound bed—a "flash effect"—directly following plasma application. This acute phenomenon likely reflects transient vasodilation and enhanced microcirculation, as documented in preclinical studies demonstrating electric fields and reactive oxygen and nitrogen species–mediated endothelial activation and increased perfusion.[9,28,29] Although this short-lived vascular response did not result in accelerated granulation under the current dosing schedule, it supports the

Table 5. Pain Scores (VAS) for Control and Experimental Groups at Weeks 0, 4, and 9

Group	N	Mean	SD	p50	p25	p75	Minimum	Maximum
Week 0								
Control	25.00	2.92	3.68	1.00	0.00	6.00	0.00	10.00
Experimental	27.00	3.44	3.52	2.00	0.00	6.00	0.00	10.00
Total	52.00	3.19	3.58	2.00	0.00	6.00	0.00	10.00
$P = 0.5777$; $P(e) = 0.5830$								
Week 4								
Control	25.00	1.52	2.82	0.00	0.00	2.00	0.00	10.00
Experimental	27.00	2.22	2.89	1.00	0.00	4.00	0.00	10.00
Total	52.00	1.88	2.85	0.00	0.00	3.00	0.00	10.00
$P = 0.1988$; $P(e) = 0.2035$								
Week 0								
Control	21.00	3.29	3.85	2.00	0.00	7.00	0.00	10.00
Experimental	20.00	3.45	3.49	3.00	0.00	6.00	0.00	10.00
Total	41.00	3.37	3.63	2.00	0.00	6.00	0.00	10.00
$P = 0.8921$; $P(e) = 0.8996$								
Week 9								
Control	21.00	1.00	1.97	0.00	0.00	0.00	0.00	6.00
Experimental	20.00	2.05	3.28	0.00	0.00	3.00	0.00	10.00
Total	41.00	1.51	2.71	0.00	0.00	3.00	0.00	10.00
$P = 0.2618$; $P(e) = 0.2697$								

Descriptive statistics (mean, SD, median, interquartile range, minimum, maximum) and P and permuted $P(e)$ values are shown for each time point.

Table 6. Summary of Treatment Outcomes for the Control (SOC) and Experimental (Air CAPJ) Groups, Including Wound Area Reduction, Quantitative Microbial Load, and Granulation Tissue Scores Across Follow-up Visits

Variable	Week	SOC (Mean ± SD/Median)	Air CAPJ (Mean ± SD/Median)	*P*
Wound area reduction, %	0 (baseline)	14.2 (SD 18.6) cm^2	13.2 (SD 18.2) cm^2	0.50
	4	–36.1%	–41.8%	0.98
	9	–42.9%	–42.5%	0.75
	17	–56.7%	–72.9%	0.30
Granulation tissue score (0–3)	0 (baseline)	0.62 ± 0.50	0.64 ± 0.49	0.8361
	4	1.35	1.50	0.4395
	9	1.64	1.93	0.1327
	17	1.92	1.96	0.8298
Quantitative microbial load, CFU, ±SD	0 (baseline)	$3.8 \times 10^6 \pm 1.2 \times 10^7$	(Pre-CAPJ) $1.1 \times 10^6 \pm 4.4 \times 10^6$ (Post-CAPJ) $5.8 \times 10^5 \pm 2.9 \times 10^6$	0.352 0.016
	4	$6.0 \times 10^6 \pm 1.8 \times 10^7$	(Pre-CAPJ) $2.5 \times 10^6 \pm 6.8 \times 10^6$ (Post-CAPJ) $1.8 \times 10^5 \pm 9.0 \times 10^5$	0.216 0.014
	9	$1.2 \times 10^6 \pm 3.3 \times 10^6$	(Pre-CAPJ) $4.7 \times 10^5 \pm 1.2 \times 10^6$ (Post-CAPJ) $4.9 \times 10^5 \pm 1.6 \times 10^6$	0.879 0.736

Descriptive values for each outcome measure are presented for both groups at the corresponding time points.

biological plausibility of CAP's prohealing properties and merits further investigation using real-time perfusion imaging or tissue oxygenation monitoring.

Antimicrobial Activity

Quantitative and qualitative cultures demonstrated a rapid and statistically significant reduction in bacterial load immediately after CAP treatment, with mean score decreases of 31.8% at week 0 ($P = 0.001$), 31.2% at week 4 ($P = 0.001$), and 18.7% at week 9 ($P = 0.046$). These outcomes are consistent with the 34% reduction reported by Isbary et al[24] and outperform results from smaller cohorts such as Brehmer et al.[25] However, the fixed 4-week sampling interval limits the ability to define the exact duration of the antimicrobial effect. Future studies with more frequent microbiological assessments are needed to better characterize recolonization kinetics following plasma therapy.

Patient-reported Outcomes and Safety

Both groups reported high aesthetic satisfaction at week 17, with no statistically significant differences, indicating that CAP does not compromise cosmetic outcomes or patient acceptance. Pain scores (VAS) decreased progressively in both arms, and intergroup comparisons showed no additional discomfort attributable to plasma application. Notably, no serious AEs were linked to the device, and nonserious AEs were mostly transient sensations such as stinging or cramping during application—consistent with the established tolerability profile of CAP.

Strengths and Limitations

Key strengths of this trial include its prospective, randomized design and multicenter nature, and the use of a portable and consumable-free CAP device. The trial was independently conducted across 4 centers, approved by

the Spanish Agency of Medicines and Medical Devices, and subjected to internal and external audits to ensure methodological rigor and regulatory compliance. Limitations include a smaller-than-planned sample size and uneven recruitment across sites, especially in the control group, which may have reduced statistical power.

Clinical Implications and Future Directions

Air CAPJ seems to be a noninvasive adjunct or alternative to standard VLU care, offering both antimicrobial and prohealing benefits without pain or adverse effects. Future research should:

1. Increase sample size and extend follow-up to assess long-term healing durability and safety;
2. Optimize treatment parameters, exploring varied dosing regimens, frequencies, and combinations with other dressings;
3. Investigate mechanistic pathways using real-time imaging (eg, laser Doppler flowmetry) to quantify microcirculatory effects and correlate with clinical outcomes.

CONCLUSIONS

This clinical trial highlighted the promising potential of PlasmAction Med for treating chronic VLUs. Although the primary efficacy endpoint did not reach statistical significance, the experimental group achieved a 16.25% greater reduction in ulcer area compared with the control group, exceeding our predefined 10% threshold for clinical relevance and suggesting an accelerated healing effect. Compared with SOC, PlasmAction Med showed a consistent decrease in bacterial load and demonstrated an excellent safety profile, with no device-related AEs or increases in pain. These findings support air cold plasma therapy as a viable, non-invasive, patient-friendly alternative to conventional wound care, combining both decontamination and prohealing actions. Future trials with larger cohorts are warranted to expand these findings, paving the way for their integration into routine clinical practice for chronic VLUs.

Bernardo Hontanilla, MD, PhD
Department of Plastic and Reconstructive Surgery
Clínica Universidad de Navarra
C/ Pío XII 36
31008 Pamplona, Spain
E-mail: bhontanill@unav.es

DISCLOSURES

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