Treatment of chronic wounds with cold plasma: a randomised, single-blind, placebo-controlled clinical study

Objective: This study aimed to investigate the wound healing properties of cold atmospheric plasma (CAP) in patients with chronic wounds.
Method: This was a prospective, multicentre, two-arm, randomised, single-blind clinical study which compared the wound healing treatment of CAP with placebo, both of which were combined with best practice wound care.
Results: The study cohort consisted of 70 patients: 35 in the CAP group and 35 in the placebo group. There was a statistically significant ($p<0.0001$) reduction in the wound area at the end of the study, and faster wound healing, with the use of CAP compared with a placebo device.
Conclusion: The results of this study showed that without requiring adjunctive therapies, the CAP device represents a safe, well-tolerated, and highly effective therapeutic option for wounds in that it promotes their rapid healing.
Declaration of interest: The study was performed under a research grant from terraplasma medical GmbH, Germany. The cold atmospheric plasma device (plasma care; terraplasma medical GmbH, Germany), placebo device (placebo device; terraplasma medical GmbH, Germany) and spacers were funded by terraplasma medical GmbH. RS has acted as a consultant to terraplasma medical and to neoplas med GmbH, Germany. LG is an employee of terraplasma medical GmbH. The other authors have no conflicts of interest to declare.

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Chronic wounds are one of the major public health challenges making skin treatments a growing problem worldwide.[1] The global burden for wound management has increased rapidly in the last 10 years, negatively impacting patients' quality of life (QoL), causing pain, mobility restrictions and psychological stress, but also imposing high costs for its treatment.[2] The treatment of chronic wounds remains a challenge in clinical practice, even with modern wound dressings and specialised healthcare professionals. The treatment of chronic wounds requires new approaches that take into account the complexity of the wounds and their underlying disease.

Cold atmospheric plasma (CAP) has emerged in recent years as a promising wound healing treatment. CAP is generated via the ionisation of atoms in a gas, generally by exposure to strong electric fields, and consists of ions, free radicals and molecules at varying energy states. Reactive species generated by CAP can react with healthy human cells and stimulate intracellular processes.[3–6]

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One reason for CAP's promising results in wound healing can be attributed to its antibacterial property; it can inactivate bacteria and fungi, including antibiotic-resistant bacteria.[7–14] This is especially important in chronic wounds as they have a high risk of bacterial and fungal infections.[15,16]

At the cellular level in mammalian cells, CAP generates oxidative stress, which activates intracellular pathways for cell regeneration and growth.[17–19] The synergistic relationship between the activating effect on healthy human cells and an inactivating effect on bacteria and fungi stimulates healing of wounds.[15,17,20,21] The positive outcome of CAP in wound management has been measured by the rate of wound healing and scar recovery,[22] where it has not only increased the rate but also reduced the redness, roughness and itching of the skin.[23,24] Plasma treatments have shown promising results in studies and case reports for wound healing, bacterial inactivation, and even cancer cell therapy, all within a similar timeframe, allowing for the specific device used. This suggests that simultaneous bacterial inactivation and wound healing stimulation can be achieved.[25–27]

Another reason for the wound healing properties of CAP is its ability to reduce wound pH.[28–30] In the process of wound healing, the pH of the wound is an important factor. The functions of most human cells are optimised for a physiological pH (7.4), ranging from slightly acidic to slightly alkaline, but not strongly alkaline as is common in chronic wounds.[30,31] A strongly alkaline pH in chronic wounds will allow bacterial growth.[28–30] It has been reported that the pH of the bacterial environment

fluctuates after CAP treatment, mostly tending towards acidification.[30,32,33] CAP-induced changes in the pH environment are beneficial for the inhibition of bactericidal activity, especially under acidic conditions.[34–36]

The benefits of CAP in chronic wound healing have been demonstrated in clinical studies. Strohal et al.[29] found that granulation tissue formation was significantly higher compared with control, the wound area reduced significantly faster and the pH value decreased significantly faster, overcoming the local infection more rapidly with CAP treatment. The wounds included in this study were between 0.26–45.15cm², with an median of 3.68cm².

CAP is safe to use and has no mutagenic effect on healthy human cells.[37,38] The high effectiveness of CAP can be observed even against bacteria that have already developed resistance to conventional agents (including antibiotics and antiseptics); this is due to CAP using a combination of reactive oxygen and nitrogen species which attack multiple cellular targets simultaneously.[13,39–41] This multi-target mechanism makes it difficult for bacteria to develop resistance, as they would need to evolve defences against several damaging factors at once. Unlike traditional antibiotics, which often target a single metabolic pathway, or antiseptics that act via unimodal mechanisms such as protein denaturation or membrane disruption, CAP's multimodal action overwhelms bacterial repair systems. Although antiseptic resistance is clinically less common than antibiotic resistance, bacteria can develop tolerance to conventional disinfectants (e.g., via efflux pumps or enzyme production).[36,42]

Various medical devices with different technologies to generate CAP for medical use exist. For example, dielectric barrier discharge uses insulated electrodes to produce non-thermal plasma at atmospheric pressure. Another is plasma jets, in which a carrier gas (e.g., helium/argon) flows between high-voltage electrodes, emitting a directed plasma plume at low temperatures.[43,44] The device used in this study uses surface microdischarge (SMD) plasma, which is generated by applying high voltage across electrodes on a dielectric surface, creating localised discharges at atmospheric pressure. In this study, a CAP device (plasma care; terraplasma medical GmbH, Germany) was used. It is based on SMD technology. This allows the production of plasma without a supply of carrier gas and therefore for a mobile device. The size of the electrode is designed to homogeneously treat an area of about 13cm², where the dose is dependent on the duration of treatment.

Based on the promising potential of CAP in chronic wound treatment, the present study aimed to investigate the wound healing properties of the medical CAP device plasma care. The major study question was whether wound healing in chronic wounds of all stages and causes with CAP is significantly superior to placebo treatment (placebo device and best practice wound care). Various parameters important for wound healing (e.g., infection control, lowering of pH value, reduction of exudate) were also observed and analysed alongside the patient-related outcome parameters of pain, sensation during therapy and tolerability.

Methods

Study design and patients

This was a prospective, multicentre, two-arm, randomised, single-blind clinical study. It was conducted in two study centres in Austria: the Federal Academic Teaching Hospital, Feldkirch; and the Academic Teaching Hospital, Bregenz. The recruitment of eligible patients took place between 1 April 2023 and 31 October 2023.

The study is registered on clinicaltrials.gov as: NCT07050667 (https://tinyurl.com/5fe2n2z5).

Patients, who met the following inclusion criteria were eligible for study participation:

- Aged between 18–95 years at the time of consent
- A chronic wound of any origin and wound phase, including locally infected wounds
- A wound size of up to 20×10cm.

If there were several wounds per patient, one was defined as the study wound.

Exclusion criteria were:

- Patients who were pregnant and/or breastfeeding
- Patients with ongoing systemic antibiotic therapy or applied within one week before start of the study
- Patients who participated in another study within one month prior to this study
- Patients with acute wounds
- Wounds with visible tendons and bones
- Wounds with >30% dry necrosis
- Wounds with allergy or intolerance to the CAP, primary or secondary dressing
- Pressure ulcers.

Ethical approval and patient consent

The study was approved by the Vorarlberg Ethics Committee according to the Austrian Medical Devices Law (Ethic Committee EK-2-3/2023; 5 April 2023) in compliance with the ethical guidelines of the Declaration of Helsinki (1975). Informed written consent was obtained from all participants prior to the start of the study, which included for the publication of photographs.

Randomisation

Eligible patients were randomised into two study groups to receive either treatment with the CAP device (cold plasma group) or treatment with a placebo device (placebo group) using sequential block design. Confidentiality of the randomisation sequence was ensured by keeping it in sealed and numbered envelopes in the participating centres.

Both devices looked identical, including the cover/illumination of the cover. For this reason, it was not possible for the patient to distinguish the CAP device from the placebo device. Double-blinding was not possible because, in addition to the characteristic sound during plasma treatment, the CAP device also produces the characteristic ozone odour, which cannot be

imitated by the placebo device. This would be noticed by experienced CAP users; however, the patient is unlikely to recognise the smell.

Wound treatment

Similarities between the treatment groups

Both treatment groups shared several key procedures. After dressing removal, the wound was cleaned with a gauze soaked in physiological saline solution. In cases of locally infected wounds, an antiseptic or antimicrobial wound irrigation solution could be used instead of saline. If >30% fibrin coverage or dry necrosis remained after cleaning, debridement was performed before proceeding with the treatment. Both groups used a sterile spacer device attached to their respective devices, which were visually identical, including lighting and operational sounds, ensuring that the patient could not distinguish between them.

Wound care was performed according to the standard of care (SoC), using modern, wound-phase-adapted treatment approaches. The dressing was applied based on the clinician's assessment. Wounds were debrided as needed and either surgical debridement or wet–dry phase cleaning was performed. Cleaning was carried out with sterile saline solution (NaCl). The wound size was measured at baseline in all patients. The vascular status was also assessed at inclusion. Wound location was not documented, as it was not considered relevant, except in cases of pressure ulcers, which were excluded from the study.

The CAP or placebo application schedule was the same for both groups: during the first week on Monday, Wednesday, and Friday; in the second and third weeks Monday and Thursday; and from the fourth week onward on Mondays. After treatment, an appropriate primary dressing was applied based on the clinician's experience, with secondary dressings used if necessary. Dressing changes were performed at least every two days, except three days over the weekends, and daily for infected wounds. Outside of scheduled visits, dressing changes could be carried out by the investigator, general practitioner, nursing staff or by the patient themselves. Additionally, in cases of venous ulcers, both groups received compression therapy.

Differences between the treatment groups

The main difference lay in the devices used. The active treatment group employed the CAP device that emitted cold plasma during the 60-second application, whereas the placebo group used an identical-looking device that did not emit plasma, serving as a sham treatment. After treatment, the same dressing protocols were followed, with no restrictions on the use of antimicrobial therapies in the placebo group—such as silver dressings—if deemed necessary for locally infected wounds. The application of the devices was always performed by the investigator.

Infected wounds in the placebo group were cleaned using octenidine dihydrochloride (Octenisept, Schülke & Mayr GmbH, Germany). The antiseptic activity of CAP is well known;[13,39–41] therefore, no additional antiseptic interventions were permitted in this group. All wounds were treated with foam dressings or superabsorbent dressings, as needed.

Application of the CAP or placebo devices

A sterile plasma care spacer was attached to the CAP device. The device was placed on the wound with the spacer and started. The CAP device releases cold plasma and stops automatically after 60 seconds.

For larger wounds, the CAP device was used with its sterile, single-use spacer (treatment area: 13cm² per application). To ensure homogeneous coverage, the spacer was repositioned sequentially across adjacent wound areas, with each section treated for the standardised duration (e.g., 1–2 minutes). Up to six applications per session are recommended for extensive wounds, maintaining sterility by replacing the spacer after each use to prevent cross-contamination.

Importantly, this therapeutic benefit is practically achieved in clinical settings. The treatment requires only one minute per wound area during routine dressing changes, adding negligible time to SoC procedures. Furthermore, the therapy's simplicity allows delegation to existing wound care staff, such as nurses during regular bandage changes, eliminating the need for additional specialised personnel.

Assessments

Wound area, wound pH, pain, local infection, exudate level, tolerability and subjective sensation were examined at successive visits (V): day 0 (V0), day 3 (V1), day 7±2 (V2), day 10±2 (V3), day 14±2 (V4), day 21±2 (V5), day 28±2 (V6), day 35±2 (V7) and day 42±2 (V8). The treatments in both study groups are shown in Fig 1.

Study endpoints

Primary endpoint

The primary endpoint in this study was the wound size. It was investigated in four aspects, where the first was the primary study aim:

1. Wound area at the end of the study (day 42)
2. Size and time course of the wound area at the end of the study (day 42)
3. Percentage change in wound area at the end of the study (day 42)
4. Dynamics of the percentage change in wound area from baseline (day 0)

The wound area was determined digitally and automatically using the included digital patient measuring tool integrated within the patient software 'MPA' (CPM, Austria). The wound was automatically measured in cm². No manual corrections or adjustments were made to the measurements.

Secondary endpoints

The secondary parameters in this study were:

- The wound pH was measured using the skin pH meter HI 99181 (Hanna Instruments Inc., US)

- Pain as measured by a visual analogue scale (VAS) score (where 0=no pain, 10=worst pain imaginable)
- Infection, measured by the Physician Global Assessment (PGA) score (0=no signs of infection, 4= maximal signs of infection); a score of 1–4 was considered infected
- Exudate levels from 0 (absent) to 4 (very strong)
- Tolerability:
  - No problem (e.g., no maceration, deterioration of the wound, blisters)
  - New development/intensification of erythema (maceration, blisters, exudate congestion)
- Subjective sensation (1=pleasant feeling, 2=no specific sensation, 3=unpleasant, 4=very unpleasant)

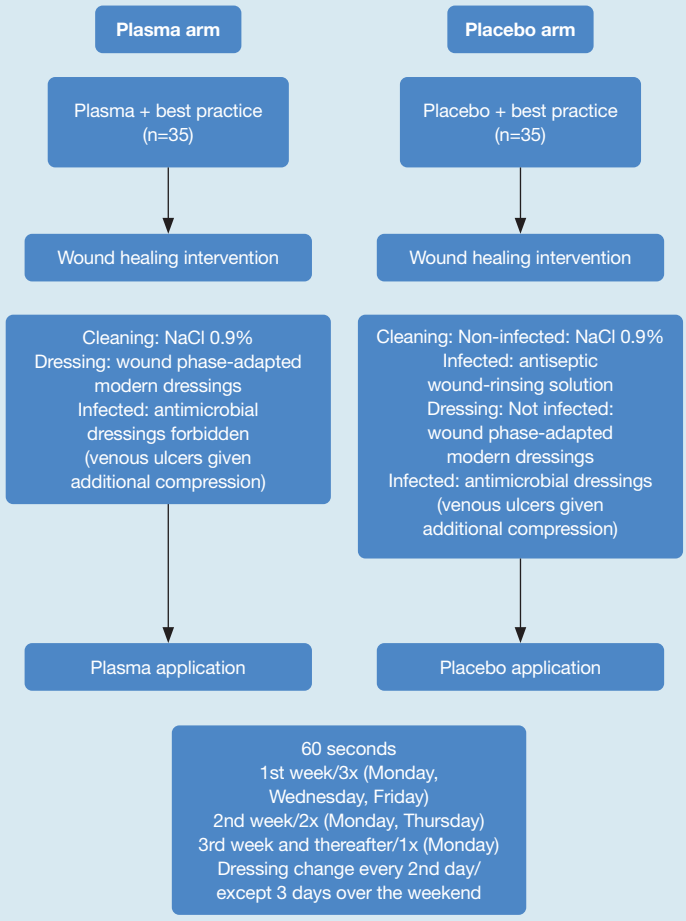
Statistical analysis

All randomised patients were included in the full analysis set according to the intention-to-treat principle. Age as baseline characteristic was described by mean±standard deviation (SD), and categorical variables were described by absolute and relative frequencies. A wound area of zero was imputed for redundant visits after healing. The primary endpoint—wound area at day 42—was analysed by an unpaired t-test after logarithmic transformations, and group differences were described with geometric means and corresponding 95% confidence intervals (CI). The percentage reduction in wound area from baseline to day 42 is described by median, minimum and maximum, and group differences were tested by the non-parametric Wilcoxon-rank sum test. pH values at day 42 were described by mean±SD and group differences were tested by an unpaired t-test. Time course modelling was performed for continuous data using a mixed linear model with repeated measurements (visits) per patient assuming a first order, autoregressive variance–covariance matrix, where visit number, treatment groups and their interaction are modelled, adjusted for the corresponding baseline values. Group differences of binary variables at day 42 were tested by the Chi-squared test and the time course was modelled by a logistic regression model. Time-to-event data are graphically shown by Kaplan–Meier curves and group differences were tested by log-rank test. All p-values are two-sided and $p \leq 0.05$ was considered statistically significant. Statistical analyses were conducted with the SAS software version 9.4 (SAS Institute Inc., US). The lineated data of the study and the statistical analysis are represented in the graphs of each section.

Sample size calculation

Sample size assumptions are based on Strohal et al.,[29] which reported log-normally distributed wound areas at day 42: a mean of 0.49±1.06cm² under experimental treatment and 3.84±7.38cm² under standard treatment. Both groups have similar coefficients of variation (~2.1), suggesting normality after log transformation. Using a t-test to detect a fold change of 2.2 in mean wound areas, 35 patients per group provided approximately 80.7% power at a 5% significance level. No drop-outs were expected. The calculation was performed with nQuery software (Statistical Solutions (https://www.statsols.com), US).

Fig 1. Representation of treatments in both study arms: The study included 70 patients, with 35 treated using the cold atmospheric plasma (CAP) device and 35 using a placebo device. Both arms followed best practice wound care with modern, wound-phase-adapted dressings. The cold plasma arm applied CAP using the device, while the placebo arm used an identical placebo device without CAP



Results

Demographics of patients

The mean age of patients in the cold plasma group was 68.21±11.48 years, and in the placebo group 67.30±12.57 years. In the cold plasma group 9/35 (25.71%) patients were male and 26/35 (74.29%) were female; in the placebo group 14/35 (40.0%) were male and 21/35 (60.0%) were female.

The majority of wounds were venous in origin, accounting for 18/35 (51.43%) in the cold plasma group and 17/35 (48.57%) in the placebo group. Peripheral arterial disease (PAD) was present in one patient in the placebo group. The distribution of wound types included a mixed aetiology in 11/35 (31.43%) of the cold plasma group and 16/35 (45.71%) of the placebo

group. Diabetes was present in 5/35 (14.29%) of patients receiving cold plasma therapy, compared with 1/35 (2.86%) in the placebo group. One patient in the placebo group had an ulcer of unknown aetiology.

Wound area

The use of the CAP device significantly reduced the wound area (geometric mean 0.012cm^2; 95% CI: 0.004, 0.034) in comparison with the placebo device (geometric mean 0.805cm^2; 95% CI: 0.362, 1.787) by day 42 (end of the study (Fig 2); p<0.0001).

The dynamic of the wound area measured throughout the visits (V0 (day 0) to V8 (day 42)) and at day 42 displayed a significantly faster decrease with CAP than with placebo (p=0.0007; Fig 2). The average decrease in size of the wound area per visit in the cold plasma group was 0.70cm^2 whereas in the placebo group it was 0.36cm^2.

The wound area expressed as a percentage of the initial value at V0 (day 0) was significantly smaller with the use of the CAP device (median 0%; minimum 0%, maximum 30.8%) than with the placebo device (median 35.2%, minimum 0%, maximum 189.3%; p<0.0001) measured at day 42 (V8) (Fig 3).

The average percentage decrease in wound area in relation to the initial size was significantly greater with CAP than with placebo (p<0.0001), 10.9% in the cold plasma group and 6.4% in the placebo group per visit.

Healing rate during the study period

With the CAP device, the wounds of 19/35 patients (54.3%) were healed between visits V3 (day 10)–V8 (day 42). In the placebo group wounds of only 2/35 (5.7%) patients were healed by visit V6 (day 28) (Fig 4).

The number of days to full healing (19 patients) in the cold plasma group were: day 10±2: two patients; day 14±2: one patient; day 21±2: seven patients; day 28±2: four patients; day 35±2: two patients; day 42±2: three patients.

Examples of healing progression

A comparison between the wound healing in patients in the cold plasma and placebo groups is illustrated in Figs 5, 6 and 7).

In the placebo group, the wound healing progression was slower, with a slower decline in infection.

pH value

The measured pH value at each visit showed that wounds treated with CAP had a significantly lower pH

Fig 2. Absolute wound size (cm^2) over time in both study groups. The CAP device significantly reduced wound area compared with the placebo device at day 42 (geometric mean: 0.012cm^2, 95% CI: 0.004, 0.034 versus 0.805cm^2, 95% CI: 0.362, 1.787, respectively; p<0.0001). Wound healing was also significantly faster in the cold plasma group across all visit times (visit 0 (day 0) to visit 8 (day 42)). The boxplot illustrates the absolute wound size (cm^2) for both groups throughout the study. CAP—cold atmospheric plasma; CI–confidence interval; V—visit

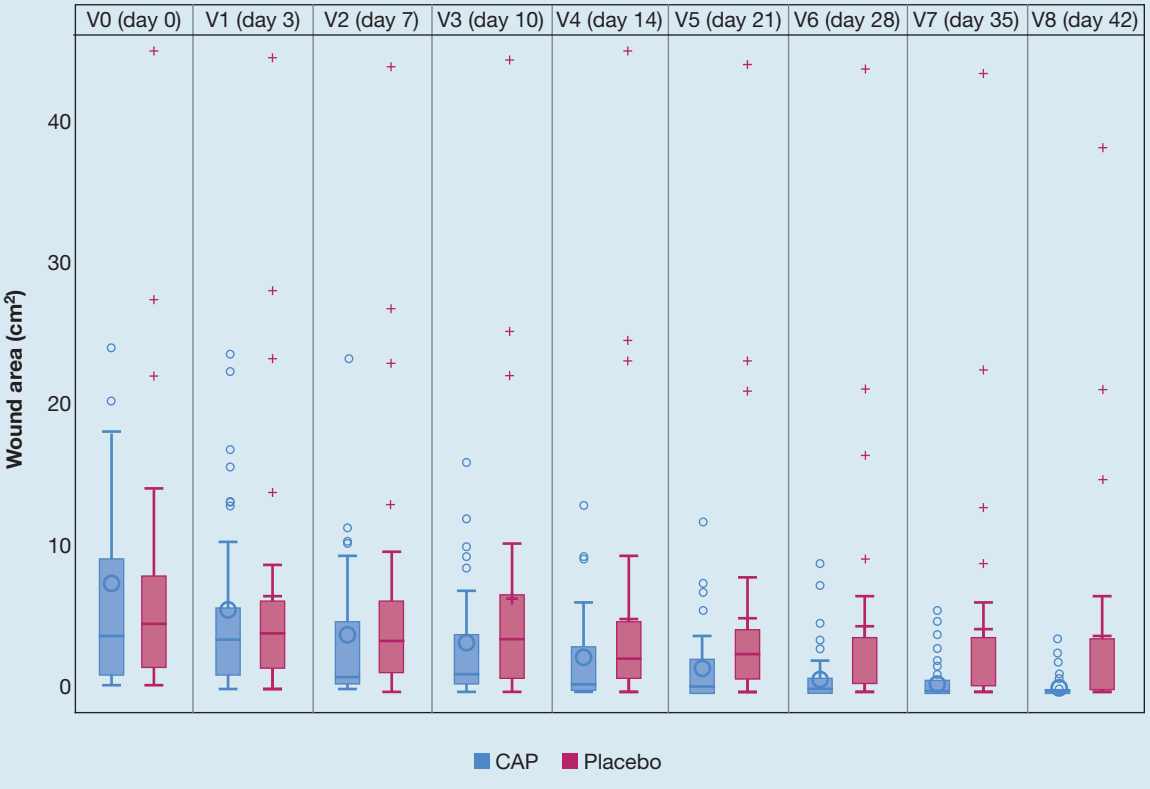
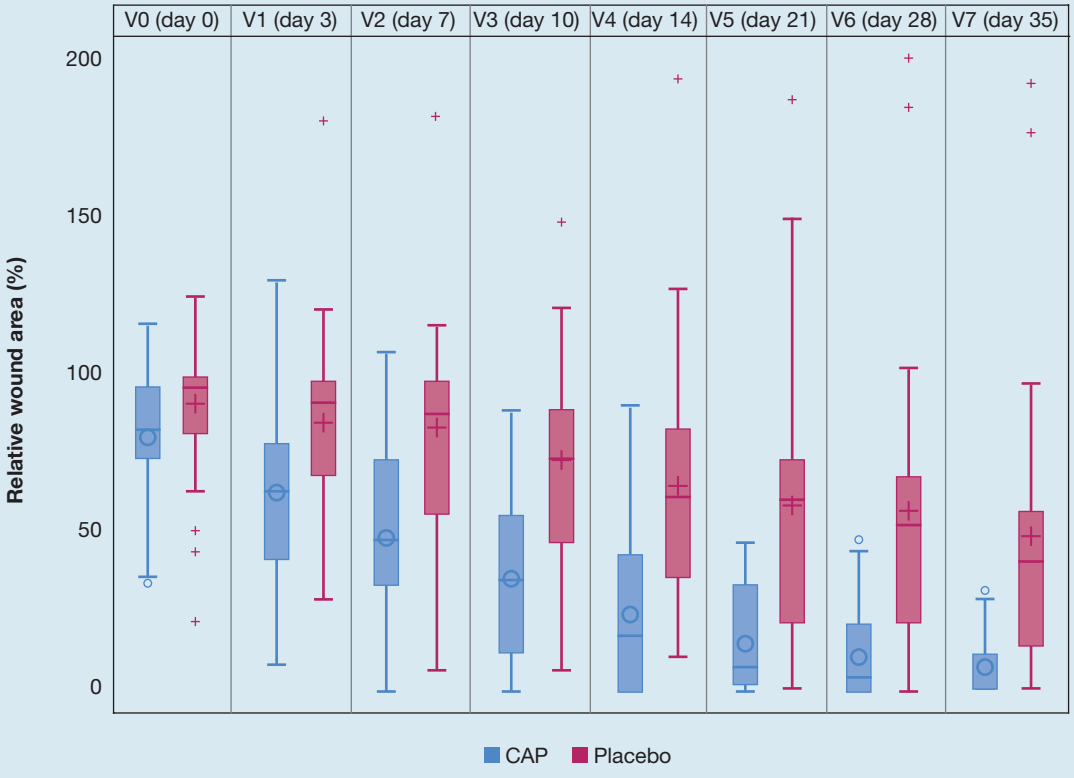


Fig 3. Size of wound area as a percentage of baseline: the average percentage reduction in wound area compared to baseline was significantly faster in the CAP treatment group than in the placebo group from visit 0 (day 1) to visit 8 (day 42) (p<0.0001). The results showed a reduction of 10.9% in the CAP group and 6.4% in the placebo group per visit. CAP—cold atmospheric plasma; V—visit



value at V8 (day 42) (7.73±0.45) compared with the placebo (9.11±0.49) (p<0.0001) (Fig 8). Furthermore, the pH decrease measured over the visits up to V8 (day 42) was significantly faster with the use of the CAP device compared with the placebo device (p<0.0001). The average pH decrease of the wound per visit was –0.26 in the cold plasma group and –0.13 in the placebo group.

Pain

Patients rated pain relief on the VAS score at each visit and the results favoured the use of CAP. At day 7 (V2) all patients treated with the CAP device scored 1 on the VAS with regard to pain relief whereas by the end of the study, day 42, pain relief was not achieved with the placebo device (Fig 9).

Infection

The infection rating on the PGA at each visit did not show a conclusive result. A possible reason could be the low number of local infections in both study groups. The number of locally infected ulcers in the cold plasma group was four, with six in the placebo group. However, the healing time was estimated to be shorter in the cold plasma group and happened within the first 10 days compared with the placebo group, where it occurred within 28 days (Fig 10).

Exudate

The rated exudate at each visit showed that at V8 (day 42) the exudate was 'healed' or 'weak' in 82.9% of patients treated with the CAP device in comparison with 17.1%

Fig 4. Complete healing within the study period: using the CAP device, wounds in 19/35 (54.3%) patients healed between V3 (day 10) and V8 (day 42), while only 2/35 (5.7%) patients in the placebo group achieved healing by V8. CAP—cold atmospheric plasma; V—visit

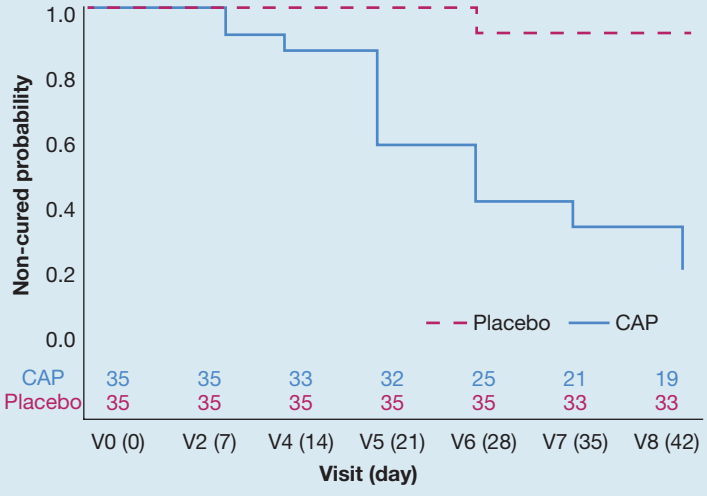


Fig 5. Example of healing progression of patient number 2 in the cold plasma group. V—visit

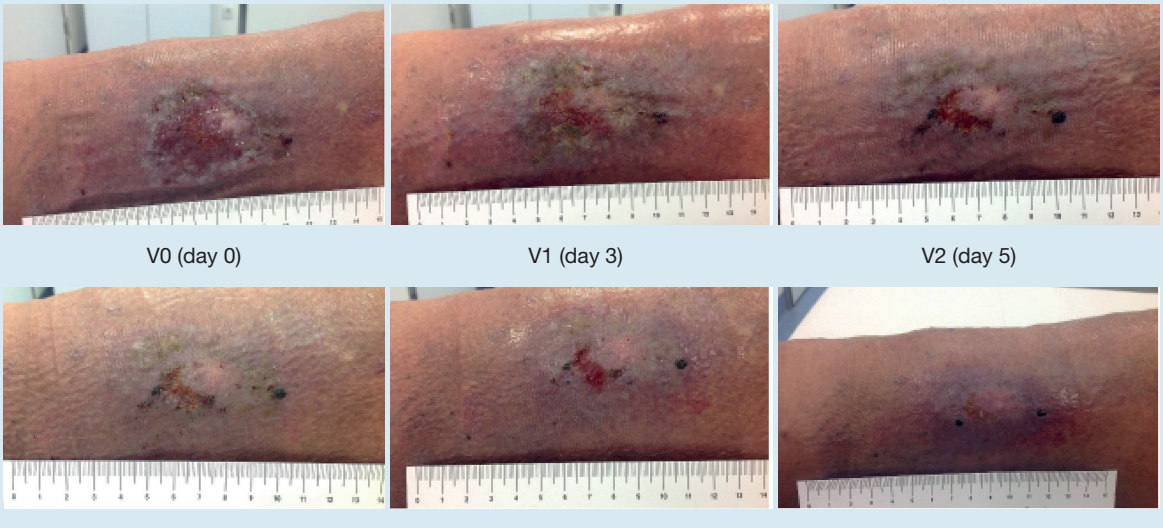
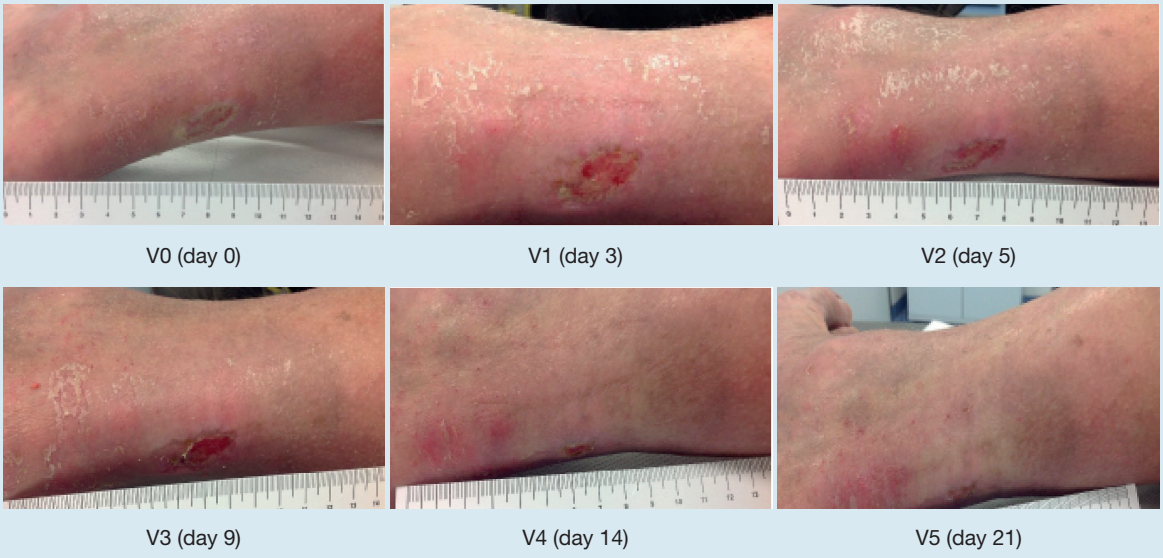


Fig 6. Example of healing progression of patient number 6 in the cold plasma group. V—visit



of patients treated with the placebo device ($p<0.0001$) (Fig 11). Patients treated with CAP had a significantly higher chance of reaching 'healed' or 'weak' status earlier than the patients treated with the placebo ($p<0.0027$).

Tolerability

Both the CAP device and the placebo device were tolerated without any problems at each visit, indicating that the CAP device was safe to be used (Fig 12).

In each case, only one ulcer (in the placebo group at V3 (day 10) and in the cold plasma group at V7 (day 35)) showed reddening.

Subjective sensation

Patients were asked to rate the sensation at each visit. The results were similar for both groups: all patients responded 'no specific sensation' at each visit (Fig 13).

Discussion

The present study aimed to advance the understanding of chronic wound healing by comparing the efficacy of two treatments: CAP generated by the CAP device versus a placebo device, both administered alongside best practice wound care.

The presented results demonstrate the significance of CAP treatment in comparison with the placebo, indicating superiority of the CAP device in management of chronic wounds. Namely, the wounds treated with the CAP device decreased in size significantly more than those treated with the placebo device at the end of the study period. As the area of the wound was measured

digitally and automatically, no bias by the examiner could have influenced the results. Additionally, statistically significant faster healing over time (from randomisation V0 (day 0) to V8 (day 42)) was observed for CAP treatment along with percentage decrease in wound area compared with the initial size. The significant reduction in the pH value at the final visit with CAP treatment, which facilitates the wound healing process, was also observed. During the wound healing process, normalisation of the exudate in a significantly larger number of patients was reached in the cold plasma group compared with the placebo group. CAP treatment led to pain relief by the third day, whereas no pain relief was reported with the placebo treatment. Regarding the safety assessments, no adverse events or serious adverse events occurred during the study period. Taking into account that CAP treatment was well tolerated and did not cause any sensations beyond perhaps a little warmth or similar in the patients, there is high potential for the CAP device in chronic wound management.

The prolonged alteration of pH in a wound environment by CAP is a fascinating aspect of its therapeutic potential. While the immediate effects of CAP are primarily due to reactive species, such as reactive oxygen and nitrogen species, these can also trigger a cascade of intracellular processes that extend beyond the initial treatment. The pH drop can be mainly attributed to acidic species originating from the precursor nitric oxide (NO) that generates nitric acid (HNO_3) and nitrous acid (HNO_2) in solution.[45] Reactive species generated by CAP can activate various cellular pathways, including those involved in inflammation, cell proliferation and tissue regeneration.[43,46] These intracellular processes can influence the local biochemical environment, including the regulation of the pH value.[47] For example, the activation of certain enzymes and signalling pathways can lead to increased metabolic activity or changes in ion transport mechanisms which, in turn, can sustain an altered pH level over a longer period. Moreover, CAP treatment can induce modifications in the wound exudate and tissue matrix, affecting the buffering capacity of the wound environment.[29,48] These changes can help maintain a more acidic pH for an extended duration. This sustained pH shift can be beneficial, as an optimal pH is crucial for effective wound healing, antimicrobial activity and tissue regeneration.[34,39]

In summary, while the reactive species from CAP have an immediate impact, their ability to stimulate intracellular processes and modify the wound environment can prolong pH changes. This extended influence enhances the overall healing process, making CAP a promising tool in wound management.

Concerning the reduction of local infections, conclusive results could not be reached as there were a limited number of infected wounds included in the study. Local infection was assessed by using a PGA scoring system and well-established clinical criteria, such as impaired fragile granulation tissue, increased exudate levels, increased pain and impaired wound healing.[29,49–51] Although the PGA is not a clinical parameter defining the development of local infection in routine clinical treatment, it represents an excellent study parameter. It allows the experienced investigator to assess the signs of local infection equally at the same time. The assessment of the development of local wound infections with the PGA score has already been successfully applied in other studies.[29,52]

The findings of this study have added to the growing body of evidence supporting the wound healing

Fig 7. Example of healing progression of patients numbers 7 (upper row) and 3 (lower row) in the placebo group. V—visit

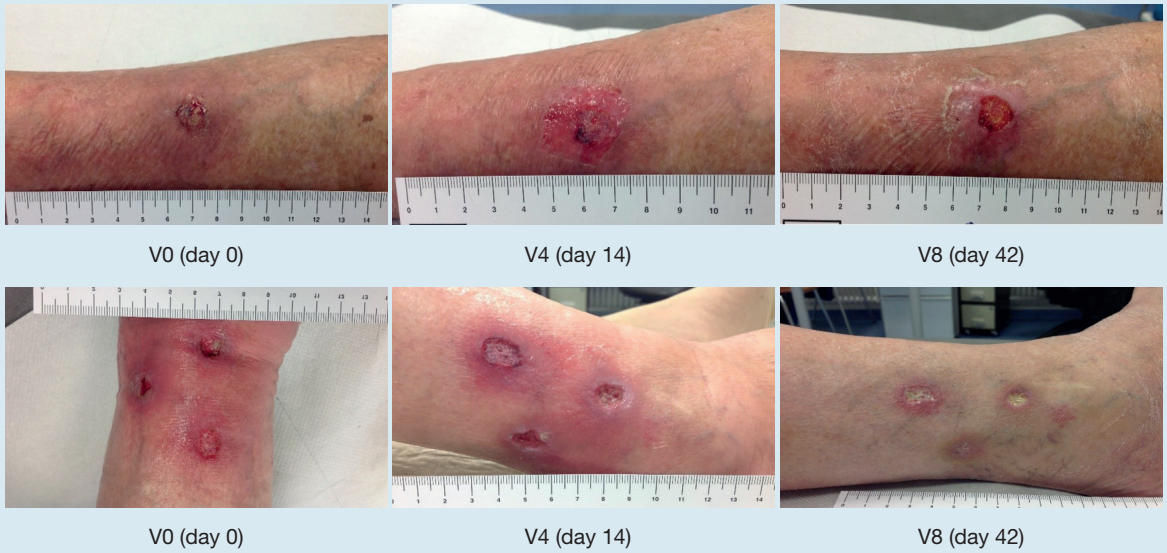
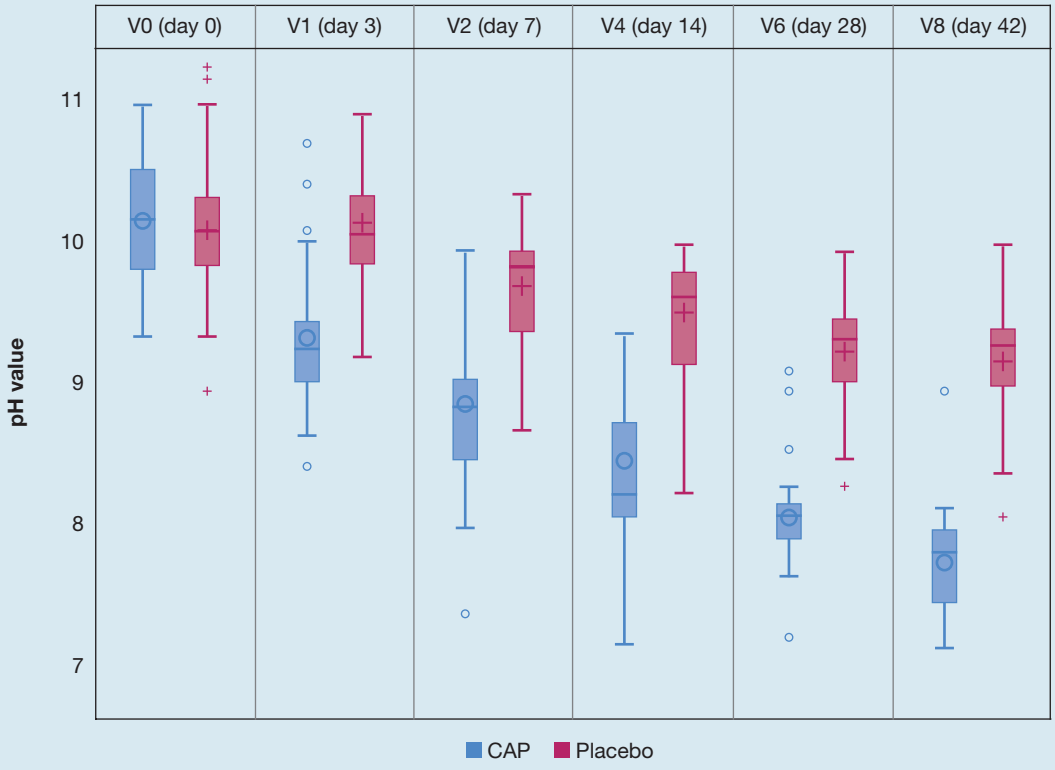


Fig 8. Average pH value: the boxplot shows the pH value of wounds over the visits (V) up to V8. Wounds treated with CAP had a significantly lower pH value at V8 (day 42) (7.73±0.45) compared with placebo (9.11±0.49, p<0.0001). The decrease in pH was significantly faster with the plasma device (average –0.26 per visit) than with placebo (–0.13, p<0.0001). CAP—cold atmospheric plasma; V—visit



capacity of CAP by demonstrating a larger decrease of the wound area along with reduced duration of the healing process. The effectiveness of CAP in wound healing is supported by Strohal et al.[29] as well as by other authors.[7,15,16,20,53] In particular, the comprehensive paper, 'Cold plasma: an emerging technology for clinical use in wound healing'[6] by the European Wound Management Association, is a sign of the emerging recognition of this new technology. The results presented in this paper show that CAP has positive effects on wound healing, which forms the basis for its clinical application. Although further large-scale studies are needed to determine the long-term effects and optimal application protocols, the current evidence is sufficient to consider CAP a promising addition to wound treatment. These findings support the assumption that CAP could be a safe and effective option for clinical practice.

Overall, the data presented in this study showed that the treatment with the CAP device not only resulted in wounds healing faster, but also improved the pH, pain reduction and exudate parameters more quickly. This is particularly relevant for patients, since rapid improvement, especially of pain and exudate, in addition to wound healing, significantly improves their QoL as well as reducing the economic burden for the healthcare system.

Limitations

While the present study demonstrated the superiority of the CAP device over the placebo device, with a high level of evidence for key endpoints, some limitations should be acknowledged.

The single-blind design may have introduced potential bias, as the physician was aware which device was being used (CAP device or placebo). However, the identical treatment process between groups mitigated this risk, and implementing a fully double-blind design with medical devices remains technically challenging.

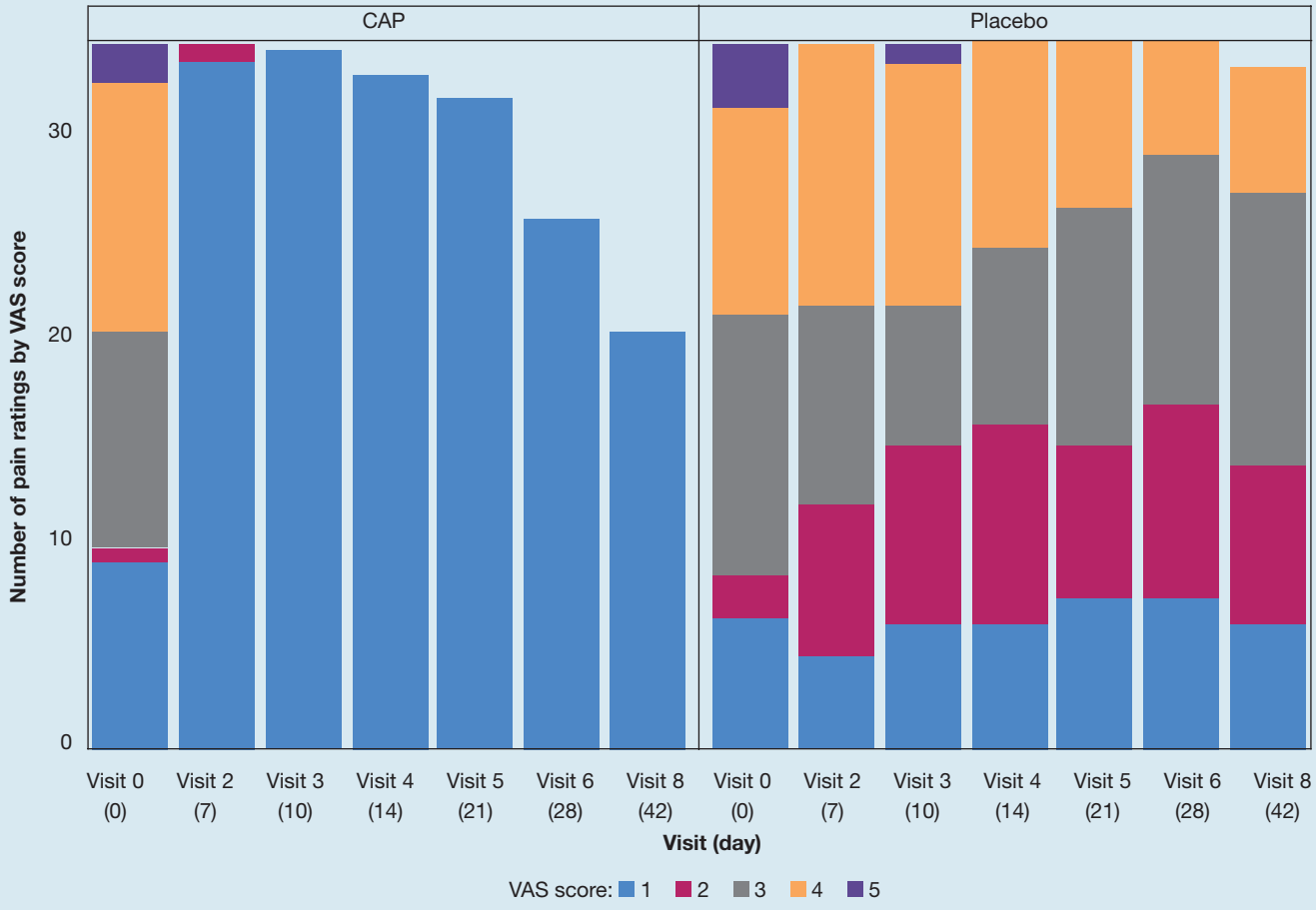
The inclusion criteria limited the number and diversity of the study population, suggesting that broader and larger patient cohorts should be examined in future research to enhance generalisability.

The limited number of infected wounds (four in the cold plasma group and six in the placebo group) can also be considered a limitation. However, the primary finding remains that CAP significantly reduced healing time compared with placebo.

Conclusion

This randomised placebo-controlled clinical study demonstrated that CAP treatment, combined with best practice wound care, not only significantly reduced wound area and accelerated healing, but also outperformed placebo treatment in key secondary

Fig 9. Pain: visual analogue scale (VAS) score. Patients rated pain relief using the VAS scale. The plasma device showed pain reduction by day 7 (Visit 2), while the placebo group had no pain relief even by day 42. A VAS score of 1 indicates clinically insignificant pain, whereas a score of 10 would indicate the worst pain imaginable. CAP—cold atmospheric plasma



outcomes: pH normalisation, pain relief, exudate management and complete wound closure.

The CAP device plasma care represents a safe, well-tolerated, and highly effective therapeutic option for wounds across various aetiologies and healing phases. Its ability to promote rapid healing without requiring adjunctive therapies may reduce treatment costs, offering both clinical and economic benefits for healthcare systems. JWC

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Fig 10. Healing of infection: Physician Global Assessment (PGA) score. The PGA infection rating did not yield conclusive results, likely due to the low number of local infections in both groups (4 in the plasma group and 6 in the placebo group). However, healing time was faster in the plasma group, occurring within by V3 (10 days) compared to by V6 (28 days) in the placebo group. CAP—cold atmospheric plasma; V—visit

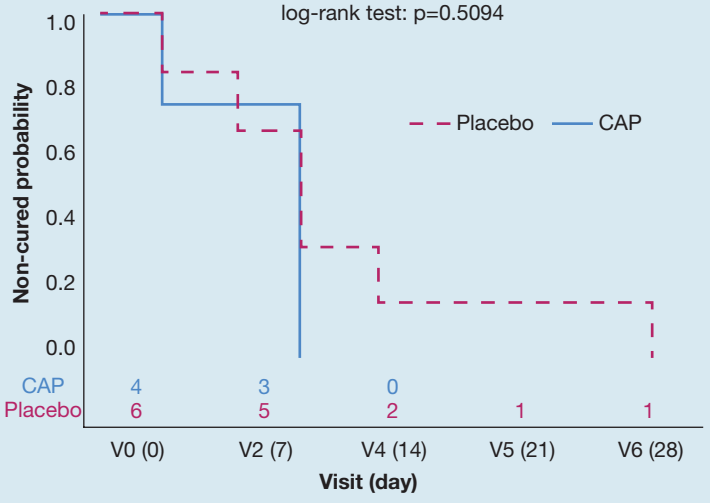

Fig 11. Exudate: by visit 8 (day 42), 82.9% of patients treated with the plasma device showed 'healed' or 'weak' exudate levels, compared with only 17.1% in the placebo group (p<0.0001). CAP—cold atmospheric plasma; V—visit

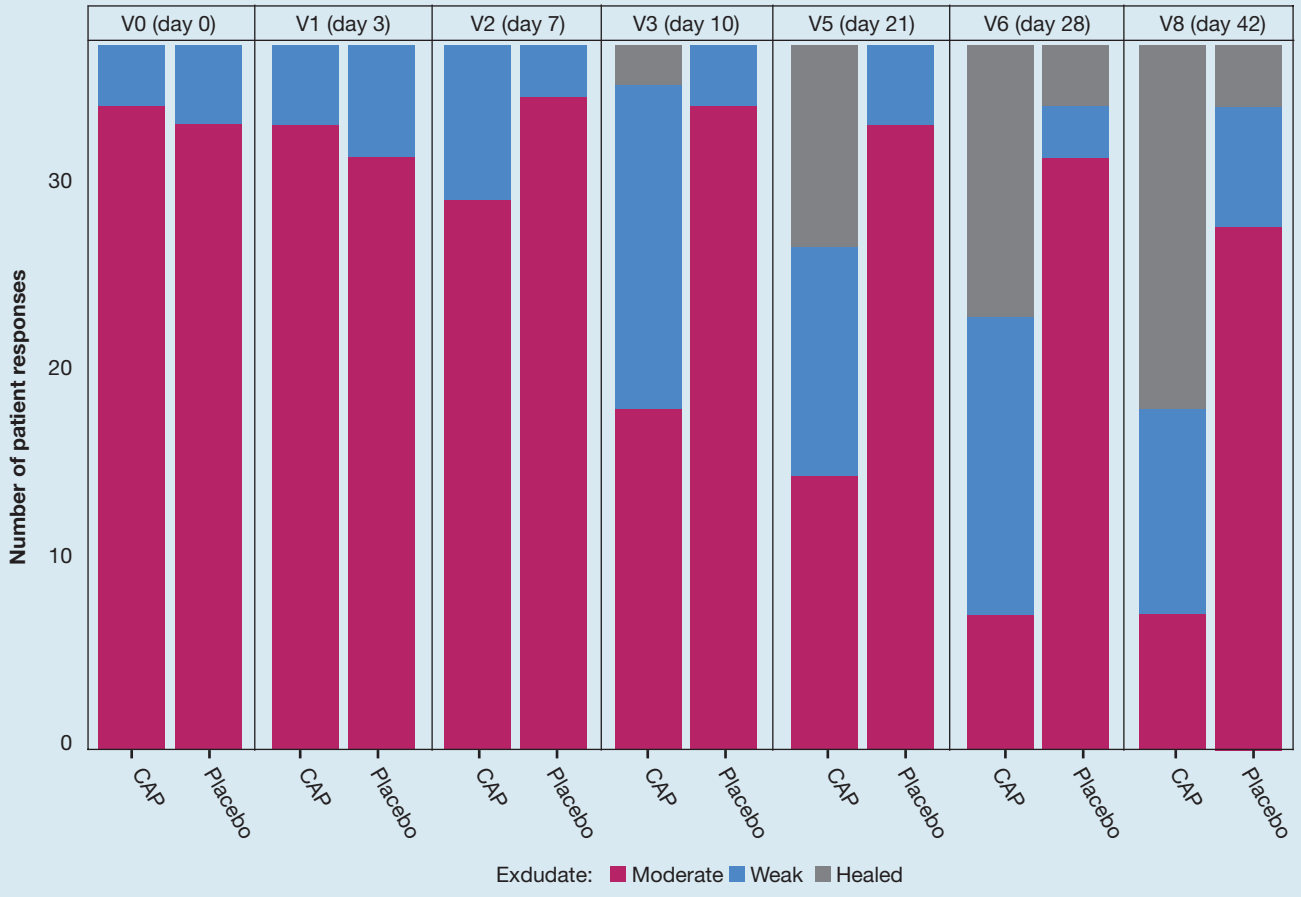

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Fig 12. Tolerability: both the CAP device and the placebo were well-tolerated at every visit, demonstrating that the device is safe for use.
CAP—cold atmospheric plasma; V—visit

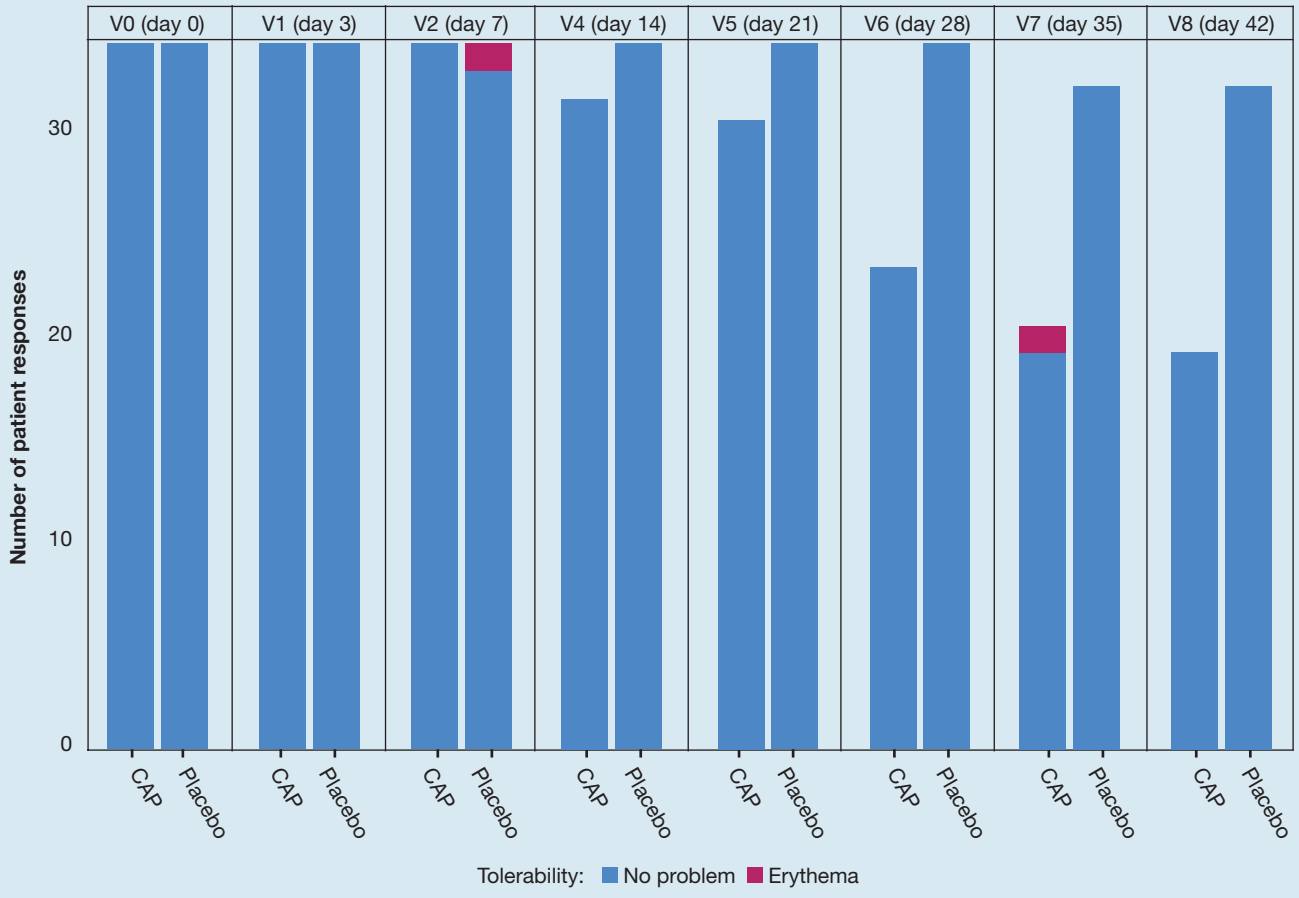

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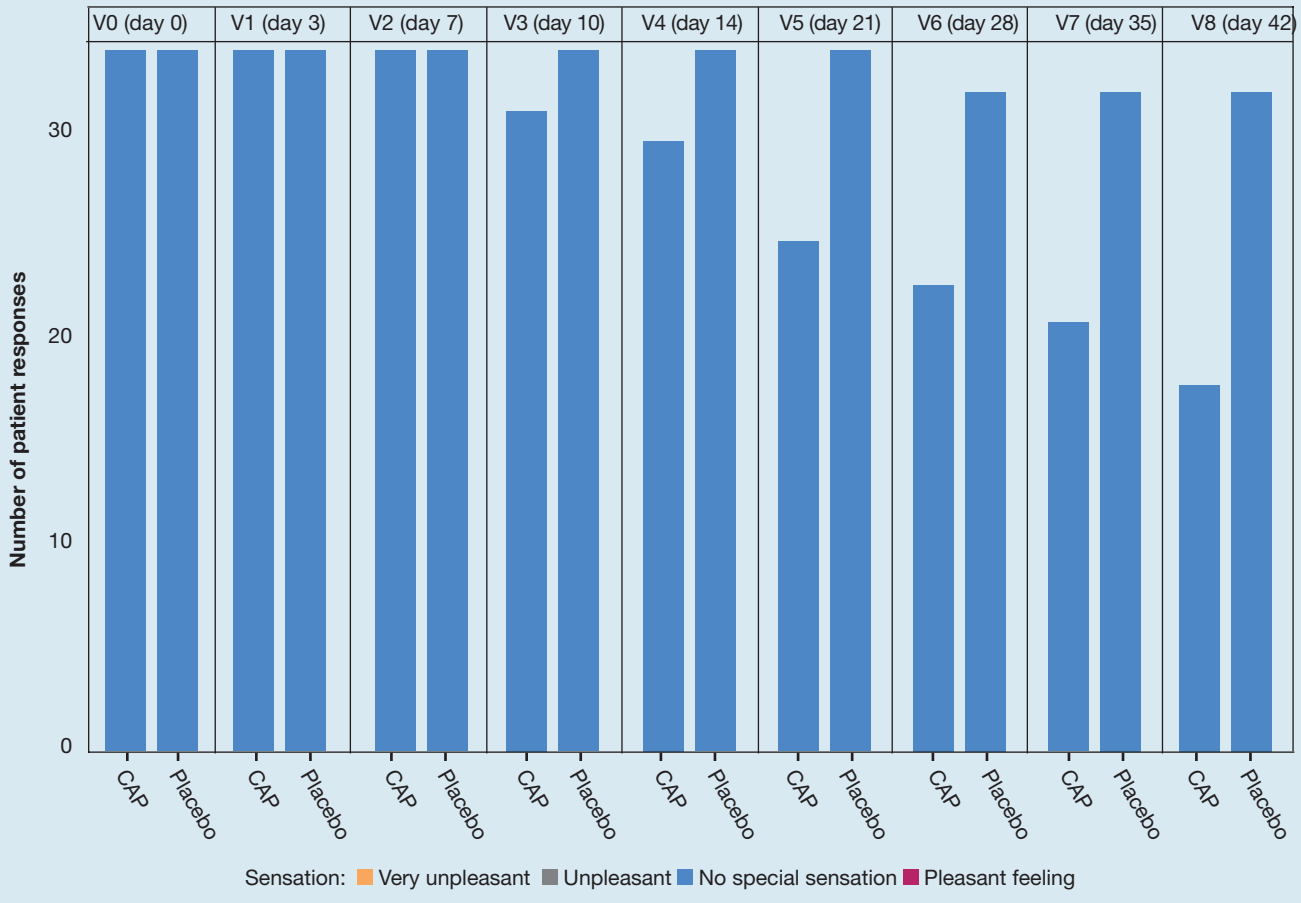
Fig 13. Sensation: all patients rated 'no specific sensation'. CAP—cold atmospheric plasma; V—visit



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Reflective questions

- Is cold atmospheric plasma (CAP) significantly better than placebo in wound healing? If so, how?
- How does the multifaceted mechanism of CAP—combining antibacterial effects, pH modulation and cellular stimulation—contribute to its potential as a comprehensive treatment for hard-to-heal wounds?
- How do the findings of this study inform the future integration of CAP devices into standard wound care protocols?
- To what extent do the significant advantages of CAP—in particular accelerated healing and pain reduction—justify the logistical effort (three applications per week over ≥6 weeks) in routine care, especially for multimorbid patients?