Positive effects of cold atmospheric plasma on pH in wounds: a pilot study

Objective: Cold atmospheric plasma (CAP) is a promising new option for the treatment of hard-to-heal (chronic) wounds. The aim of this study was to observe the effect of CAP on wound pH, as a correlation between the pH of a wound and its healing tendency has been established in the literature.
Method: Patients with hard-to-heal wounds were treated with CAP in addition to standard treatment. Treatment was performed with the aid of a small, mobile plasma device, which was used for one minute at a time during dressing changes. The pH value, wound size, and other parameters, such as exudate and signs of infection, were recorded for each treatment.
Results: A total of 10 patients took part in the study. During the observation period, there was a significant reduction in pH from a markedly alkaline pH of 9.6 to a neutral pH of 7. This was accompanied by a marked reduction in wound size by an average of 76% with seven applications of CAP within 28 days. The evaluation of tissue granulation, exudate and signs of infection showed a positive trend.
Conclusion: The number of patients in the present study is not sufficient to prove the relationship between the pH value of the wound and the treatment with CAP. However, there are clear indications that the positive effects of CAP on wound healing, which are recognised in several publications, are also due to its influence on wound pH value.
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chronic • cold atmospheric plasma • hard-to-heal • pain • plasma care • plasma medicine • wound • wound care • wound dressing • wound healing

Although advanced, wound treatment is now a standard accepted by the scientific community, yet the financing of care for hard-to-heal (chronic) wounds remains a contentious issue. Concepts that can improve the quality and efficiency of wound treatment, relieve the cost burden as well as increase patient quality of life (QoL), are urgently needed.

Regarding the care of patients with hard-to-heal wounds, cold plasma therapy seems to be a promising approach. The combination of antimicrobial properties[1–4] and the promotion of wound healing[5,6] not only helps to significantly shorten the healing time of hard-to-heal wounds,[7] but could also reduce follow-up costs, such as those related to additional medication, hospital stays, amputations and nursing.[8]

Plasma is an ionised gas, which represents a fourth state of matter in addition to solid, liquid and gas states. As with the transitions of the known aggregate states, i.e., melting and vaporisation, the transition to plasma is achieved by the addition of energy.[9] Naturally-occurring plasma such as that of the sun has extremely high temperatures,[10] therefore its use on patients is only possible due to the invention of cold atmospheric plasma (CAP), which is plasma at room temperature and atmospheric pressure.[8]

Studies have shown that CAP is able to inactivate bacteria and fungi, with the antibacterial effect being particularly noteworthy as it is also observed in antibiotic-resistant bacteria.[1,3–5,11,12] Additionally, it has been shown that CAP is able to induce wound healing.[5,6,13] On a cellular level, CAP creates oxidative stress, which activates intracellular signalling pathways that promote cell regeneration and growth up to a certain level.[14–17] Despite this, CAP has no mutagenic effect on healthy mammalian cells.[18,19]

The positive effect of CAP on wounds and various skin diseases[20–23] can therefore be attributed to a synergistic effect between the activating effect on healthy human cells and an inactivating effect on bacteria and fungi.[24,25]

It is also known that CAP is able to acidify lipid films and liquids. The skin has a protective layer, with an average pH of 5, so is slightly acidic. The composition of microorganisms living on the skin can change significantly when the acid protection of the skin is removed. Some conditions, such as atopic dermatitis, also have an increased skin pH value, and the skin is no longer protected from bacteria.[26–28] In addition, an elevated pH value over a longer period of time is a

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characteristic that has been observed in hard-to-heal wounds, while acute wounds, depending on the stage of wound healing, may temporarily exhibit an alkaline pH value but subsequently return to the acidic range.[29] Furthermore, acid-oxidising solutions used on wounds are able to promote healing.[30]

Thus, both the bactericidal and wound healing promoting effects of plasma could be related to the CAP-induced change in pH. Promising findings have been provided by a recently published study,[7] which showed that the pH value decreased in wounds treated with a plasma jet. However, since each type of plasma generation produces different plasma, this present pilot study is the first step to investigating the change of pH in wounds treated with plasma produced by surface microdischarge (SMD) technology.

Methods

This double-centric, open-ended, prospective clinical pilot study was conducted at two centres—one in Austria and another in Germany. The observation period was four weeks per patient and the study spanned from May–October 2021.

Patients and inclusion/exclusion criteria

Patients treated with CAP over a 28±2 day period were included in this pilot study.

Patients eligible for study participation had to meet following criteria: the presence of hard-to-heal wounds (by definition, wounds that persist for >6 weeks) of any origin and wound phase, including local infected hard-to-heal wounds up to a maximum wound size of 20×10cm without visible tendons and bones. In the instance of a patient presenting with several wounds, only one wound was included in the study, selected at random.

The exclusion criteria for the pilot study were: acute wounds; wounds with >30% dry necrosis; patients taking antibiotics within a week prior to the start of the study; as well as patients with an allergy or intolerance to cold plasma. Pregnant or breastfeeding women and participation in another clinical trial within the last month prior to enrolment were further grounds for exclusion.

Ethical approval and consent information

Ethical approval was not required for this study as we performed a clinical, post-marketing study with a CE-certified technical medical device according to the manufacturer's specifications. The Plasma Care device (terraplasma medical GmbH, Germany) is approved for the treatment of wounds by medical professionals.

Before the patient underwent treatment, they were asked to sign a consent form to participate in the study, and for the publication of anonymised data and photographs.

CAP device

The Plasma Care device uses SMD technology to generate CAP. In this process, an insulator is placed between a high-voltage and a structured electrode. Microdischarges between the insulator and the structured electrode generate CAP in the surrounding gas, in this case the ambient air.

A sterile spacer is placed on the device and held directly onto the wound. CAP is generated directly from ambient air within the volume defined by the spacer. The treatment is then started and automatically stopped by the device after one minute. The area of skin may be treated for a maximum of three minutes at a time.

Wound treatment

Immediately after removal of the dressing, the wounds were cleaned with 0.9% sodium chloride (NaCl) solution. If >30% of fibrin or dry necrosis was identified after cleansing, sharp debridement was carried out before the first treatment with CAP.

CAP with the plasma care device was performed using the following protocol: one minute CAP per 12cm² (this corresponds to the area of the sterile spacer). Treatment was given seven times over a 28-day period, on days 1, 3, 7, 10, 14, 21 and 28.

In the case of locally infected wounds, the application was carried out in week 1, once a day and then as for uninfected wounds from the week according to the protocol.

After CAP, the wound was covered with a non-adhering and non-active dressing (Adaptic, 3M KCI, US). The dressing change took place not only after application of CAP, but at least every second day and every third day following weekends. Dressing changes routinely occurred 2–3 times a week and daily for locally infected wounds. The application was always carried out by the nurse. In the case of a venous ulcer, a modern compression system was used.

Before each CAP treatment, the pH value of the centre of the wound or the wound fluid was measured using a pH meter (Hanna Instruments, Germany) calibrated to pH 7.

Data collection and outcome measures

The documentation of patient data and wound characteristics was initially carried out treating day 1 (D1) and for each subsequent visit, over a maximum period of 30 days (D3, D7±2, D10±2, D14±2, D21±2, D28±2).

Primary endpoint

The primary endpoint was the percentage of granulation tissue on the wound at day 30. For this purpose, the total amount of granulation tissue on the wound as a percentage of the wound area was documented at the start of the study (time 0) and at each subsequent visit. Therefore the entire extent of the wound was traced, then divided into four equal parts (one quadrant corresponds to 25%) and the amount of granulation tissue was

measured by a ruler, and the quantity of the corresponding percentage was mathematically determined.

Secondary endpoints

The secondary endpoint was the reduction of the wound area. For this purpose, the dynamics of the reduction of wound area in cm^2 were determined by a digital automated measurement system (MPA system, CompuGroup Medical AG, Germany).

The clinical signs of infection were collected with a validated infection score. Infection scores are evaluated and represent a gold standard in the documentation of infection signs.

The change in pH value was also documented. Before each dressing change, the pH value of the centre of the wound or the wound fluid was measured.

The amount of exudate was also determined. The score ranges from 0 – missing, 1 – weak, 2 – moderate, 3 – strong and 4 – very strong.

The measurement was carried out by a qualified wound specialist.

For the evaluation of the patients' QoL, the examiner asked about the patients' sensation during CAP treatment. The scores ranged from 4 – very unpleasant, 3 – unpleasant, 2 – no special sensation and 1 – pleasant feeling.

Pain and infection were assessed on appropriate scales using the VAS score (1– 0) for pain and a scale also ranging from 1 (minimum) to 10 (maximum) for infection. Exudate was scored on a scale ranging from 0 (minimum) to 4 (maximum).

The local compatibility of the treatment was assessed for safety reasons during dressing changes with the following parameters: no issues/unchanged or new formation/reinforcement of erythema, maceration, blisters or exudate congestion.

Before the new dressing was applied, a photograph of the clean wound was taken at each visit.

Results

In this pilot study, 10 patients with hard-to-heal wounds were treated with CAP in addition to standard treatment. The average age of patients was 71 years (range: 18–95 years), and five were female and five were male (Table 1). All patients had a hard-to-heal wound of venous origin on either the lower leg or ankle. The treatment with CAP was performed six times within 28 days for one minute per treated area.

Table 1. Overview of patients and treatment

Number of patients	10 (5 female, 5 male)
Average age, years	71±8
Number of treatments	7
Treatment schedule, days	1, 3, 7, 10, 14, 21, 28
Duration of treatment	1 minute per area
Type of wound	All types of hard-to-heal wounds
Location of wounds	8 in lower leg, 2 in ankle

During the treatment, several parameters related to the patients' QoL and wound healing progress were recorded, such as local tolerance of CAP and the sensation the patient experienced during application.

Regarding the CAP treatment, none of the patients recorded any unusual sensations, and so the treatment was neither painful nor unpleasant. In addition, the wound environment was also evaluated. In four patients, the wound environment was not reported to have any special features from the start of the treatment. In five patients, redness and dryness, which were noted around the wound, disappeared within three or four treatments. In one patient, the wound environment was still itchy, dry and scaly after completion of treatment.

Of particular interest was the change in wound pH value. The pH decreased from an average value of 9.67 to 7.06 (Fig 1a), which is below the physiological pH of 7.4. The pH of healthy skin is also in the acidic range and varies from person to person and also depends on the skin site.

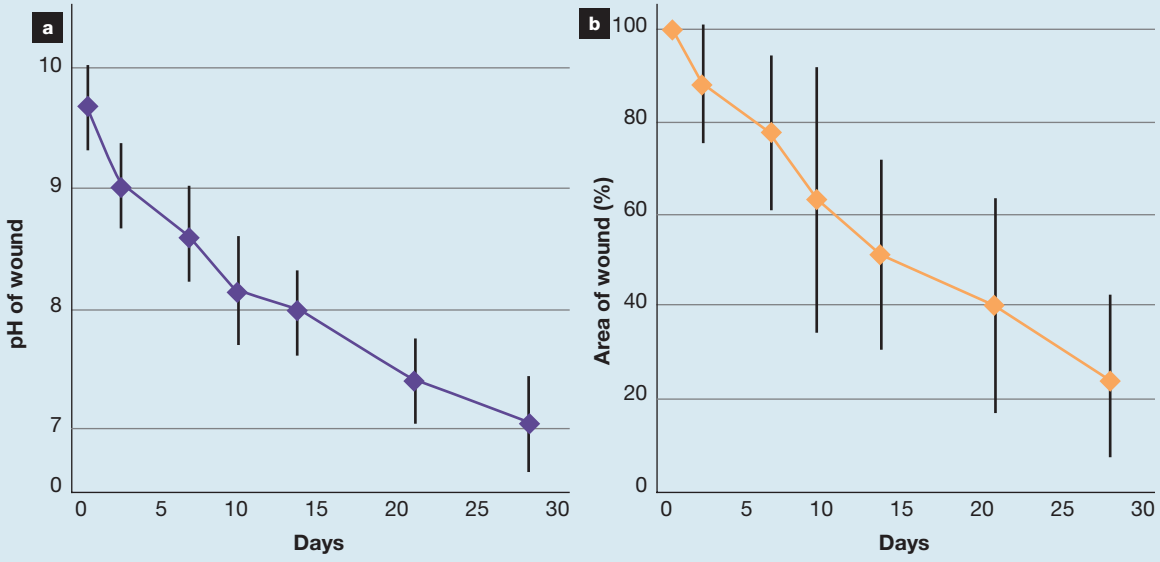
As the pH of the wound decreased, the wound itself also decreased in size. Overall, we observed a reduction in the wound area of an average of 24% of the original size. It is noteworthy that none of the wounds showed any deterioration, and six out of 10 wounds had decreased to an average of 12% of their original size after only seven CAP treatments (Fig 1b). It is expected that the trend towards complete healing of the wound will continue after the observation period and that a large proportion of the observed wounds will close completely in the near future. Further study is required to confirm.

In addition to the pH value of the wound, other parameters related to wound healing as well as the patients' QoL were observed. A particularly important parameter for patients is the sensation of pain caused by the wound. While three out of 10 patients reported their pain at only 1 on the VAS score scale of 0–10 at the beginning of treatment, another three patients had pain rated ≥5. The remaining four patients had a mean pain score of 3.1. Notably, 9 out of 10 patients reported no more pain (i.e., 0/10) within a maximum of three treatments. Only a single patient had reported a pain score of 1/10 by the end of treatment (Fig 2a).

Closely related to pain scores may also be the presence of infection in the wound. Patients were graded at a mean of 2.9±1.4 at baseline, with two patients having a higher score of up to 5. As with pain, infection decreased within a few treatments. After only four treatments with CAP, no infection was detectable in any patient (Fig 2b).

In addition, two other parameters of interest were granulation and the amount of exudate. While the granulation of the wound varied greatly from patient to patient at baseline, all wounds showed an increase in granulated area from an average of 38% to an average of 78% within the 28 days. Granulation is expected to further decrease as it is replaced by epithelial tissue until

Fig 1. Development of the pH value in the wound during the 28 days of observation. Each point represents the value on the days of CAP treatment averaged over all patients **(a)**. Average reduction of area of wound in % compared with first day of treatment. Both figures are mean+SEM **(b)** SEM—standard error of mean



complete healing is achieved (Fig 2c).

Lastly, the amount of exudate was evaluated. During the course of the study, the wound exudate decreased from an average score of 2.1 to 1.3, although significant differences were observed between the individual patients. While some wounds had little exudate at the beginning of the treatment, the amount in other patients was rated between 3 and 4 at baseline. However, in wounds with a greater level of exudate at the beginning of the treatment period, a marked decrease was observed within three treatments (Fig 2d).

During the pilot study, no adverse events (AE) or serious adverse events (SEA) were reported by the patients.

To provide a better insight into the progression of the wound healing, three of the 10 wounds are described as a representative examples (Fig 3).

Patient 1

A 68-year-old female patient with a left lower leg ulcer. Initially, the wound area was 14.8cm². The wound showed only very slight signs of infection (1) but high levels of exudate (4) and a basic pH value (9.7).

The wound responded quickly to CAP treatment. After only 14 days, the wound area had halved in size. After 28 days, the wound area reduction rate was 86%, the low signs of infection remained stable (1), the amount of exudate had reduced to a minimum (1) and the wound pH was slightly acidic at 6.1. The patient did not report any unpleasant sensations during the CAP treatment.

Patient 5

A 56-year-old female patient with a lower leg ulcer of 4.12 cm² in size, with high levels of fibrin. The amount of exudate on the first day of treatment was moderate (2). The signs of infection were described as clear (4) and the percentage of granulation tissue was 10%. The wound secretion was markedly basic at pH 9.93 and the patient reported a VAS pain score of 4.

The wound area reduced by 22% on day 10 of treatment. On day 28, there was a wound area reduction of 85%. The granulation tissue had increased to 60% and the pH value had neutralised (7.11). Signs of infection and exudation were minimal (1). The patient had reported no more pain at the end of the treatment.

Patient 9

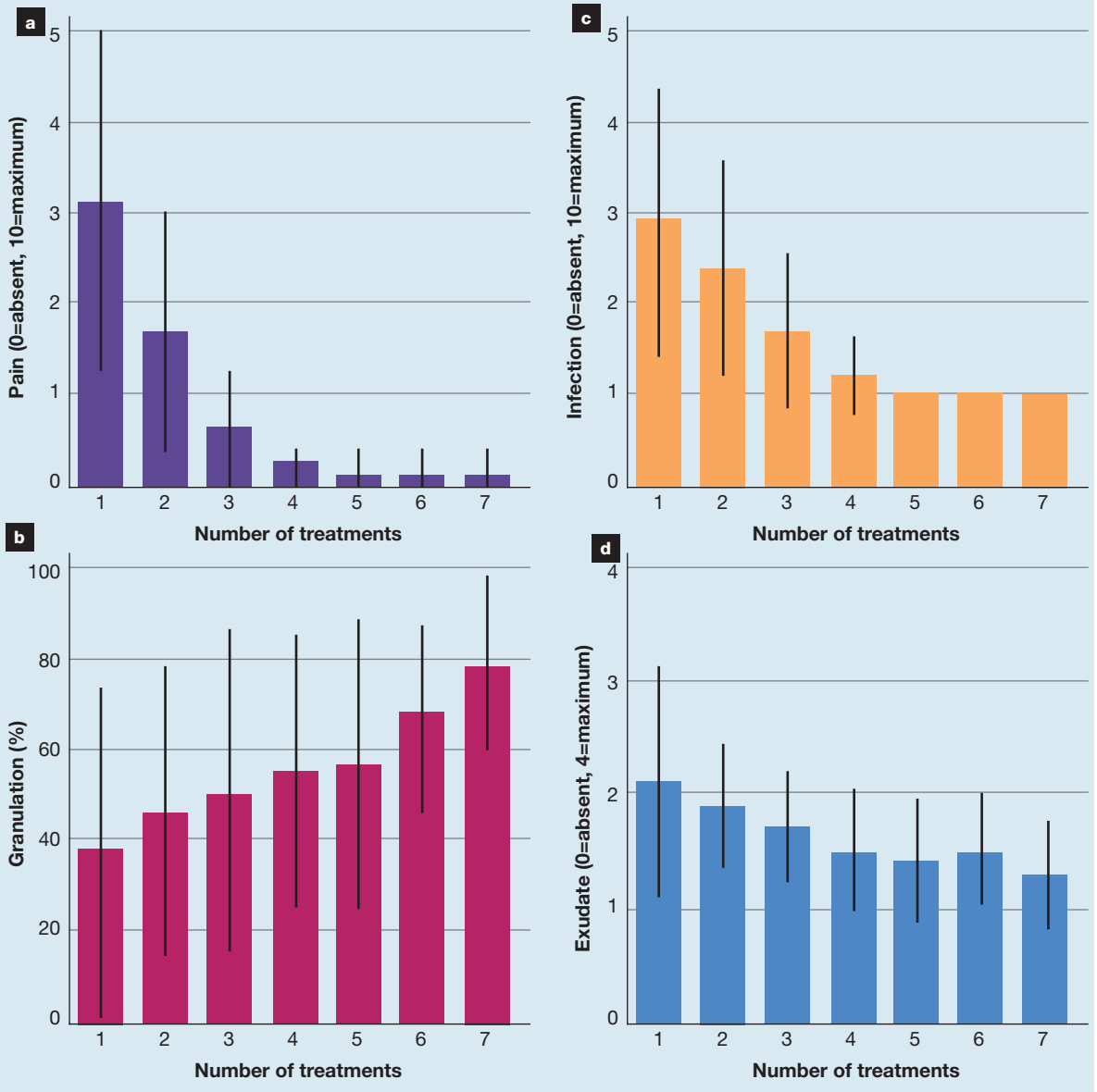
A 73-year-old female patient with a venous ulcer on the right lower leg measuring 2.75cm². Exudation was moderate at the first visit (2) and signs of infection were present (5). Only 10% of the wound surface showed initial granulation tissue. The pH of the wound was markedly basic at pH 9.8. The patient also reported pain in the wound (5). Initially, the wound was almost completely covered with fibrin and there was incipient moist necrosis at the upper right wound margin.

After 28 days, the wound area had reduced by 45% with CAP therapy. The primary goal of reduction of 75% of the original area was not achieved. Nevertheless, the wound had developed very positively, the signs of infection had decreased to 1, 90% of the wound area was granulated and the pH was neutral at 7.35. For the patient, qualitatively the most important aspect was the reduction of pain. After only one week of CAP, the pain disappeared completely.

Discussion

The treatment of hard-to-heal wounds with CAP has already been studied in several publications, in terms of bacterial load and wound healing.[5,6,31,32] In addition, interesting findings have been obtained, particularly

Fig 2. Development of different parameters during the period of CAP treatment. Reduction in pain rating (VAS score, 0–10) **(a)**, Infection (1–10 with 10 being maximum infected wound) **(b)**, average area of granulation (% of wound area) **(c)**, exudate (rated from 0–4) **(d)**. All figures are mean+SEM. SEM—standard error of the mean; VAS—visual analogue scale



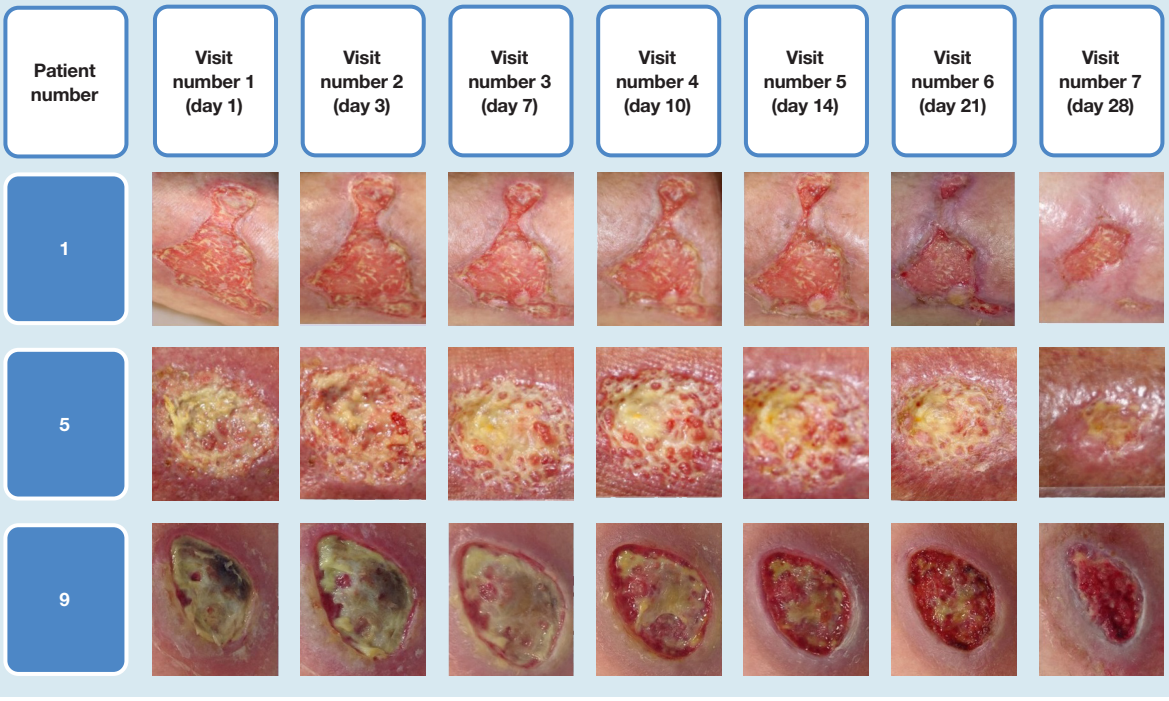
with regard to the cellular mechanisms by which CAP promotes wound healing. It was shown that CAP not only influences immune cells, but can also stimulate the formation of blood vessels.[13,14,33,34] These findings suggest that the mechanism of action of CAP is promoted by the interaction of the cells that come into direct contact with the reactive species generated by CAP with cells in deeper layers of skin.

To gain insights regarding the mechanisms of wound healing during CAP treatment, other parameters were also measured in this case study.

Of particular interest was the correlation between pH and wound healing. In a case study with a limited number of patients, despite not having a control group, correlation can be established. Since Schneider et al.[29] published the correlation between the pH of a wound and its healing stage, it has been known that, unlike acute wounds, hard-to-heal wounds remain in the alkaline range for a longer period of time. Acute wounds, on the other hand, have a basic pH during the granulation phase, but this drops again during the re-epithelialisation phase.

The change in wound pH value is often not considered. However, a recently published study was able to show that even when the wound was treated with jet plasma, the pH value dropped more quickly than in the control group.[7] These results are a promising approach to understanding the influence of CAP on

Fig 3. Healing of wounds following cold plasma treatment on the basis of representative examples



changes in pH.

During the treatment period, the pH of the hard-to-heal wounds decreased from 9.7 to 7.1, that is, from a clearly basic range to a value slightly below the physiological pH of 7.4 and closer to the acidic value of healthy skin. These findings help to better understand the impact of CAP on the wound.

CAP treatment for hard-to-heal wounds has already been shown by different studies to be efficient both in reducing bacteria and in improving wound healing.[1–8] Although many new insights into the underlying mechanisms have been discovered in recent years, the aspect of CAP that promotes wound healing is not yet fully understood.

In addition to the interaction of CAP within a single cell, the interaction of cells within the skin structure must also be considered in wound healing. For this reason, the consideration of parameters describing the condition of the wound as a whole is of great importance to understanding the mode of action of CAP. This present study was able to show that CAP can have an effect on wound pH, although it has not yet been determined whether this effect is due to changes in microbial growth. In addition, a significant decrease in infection and exudate volume was also observed, without the need for further treatment.

These results provide insights into the response of a wound to CAP therapy, but the question of the magnitude of the effect remains unanswered. To investigate this, a subsequent study with a control group would be necessary. In addition, many wounds showed a good healing tendency but had not completely closed by the end of the study. A longer treatment period and a control group would therefore be of great interest.

Limitations

The number of patients and the lack of a control group limits the power of this study. While the relationship between wound pH and healing has become more established in recent years, the relationship between CAP and pH has not yet been studied in detail. Therefore, the present study gives a strong indication of a relationship but also raises some questions that should be tested in a randomised controlled trial.

Conclusion

In summary, this pilot study provides insight into how treatment with CAP can affect the wound as a whole and reduce pH in addition to wound size and patient pain. A detailed investigation of this effect in a larger study with a control group would be desirable. JWC

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Reflective questions

- What is known about the impact of pH in wound healing?
- How can the reduction of the pH support wound healing in hard-to-heal wounds?
- How does cold atmospheric plasma support wound healing in hard-to-heal wounds?
- What is the effect of cold atmospheric plasma on the pH in wounds?