Pilot study on the influence of cold atmospheric plasma on bacterial contamination and healing tendency of chronic wounds

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Introduction

Treatment of patients with chronic wounds is an ongoing interdisciplinary challenge [1]. Currently, various treatment options are available for symptomatic wound therapy [2, 3]. Cold atmospheric plasma (CAP) has also been successfully applied in wound treatment in recent years. Plasma is the fourth physical state of matter alongside liquid, solid and gaseous. Plasma can be created by supplying a gas, such as argon, with energy. The plasma is then cooled to body temperature to be applied painlessly to wounds. The plasma contains, among other things, reactive oxygen species (ROS), ions, electrons, photons, nitrogen compounds, OH radicals and UV light.

Several clinical studies have already demonstrated good antimicrobial activity of CAP in wounds, including the eradication of multi-resistant germs [4–7]. New research approaches have also demonstrated effects on microvascularization and inflammation, suggesting that numerous other fields of application are conceivable in the future, including oncology and rheumatology [8]. With respect to wound therapy, CAP treatment in the literature ranges from three times a week to multiple times a day [9]. Due to the great variation in the devices applied, their intensity settings, treatment duration and types of application, the evidence available to date remains insufficient for determination of the best possible mode of wound therapy [10].

Summary

Background: Cold atmospheric plasma (CAP) has been used successfully for wound treatment, with thrice weekly treatment intervals. In this study, we wished to investigate whether comparably beneficial results can be achieved even with once weekly CAP treatment.

Patients and methods: In this randomized clinical pilot study (RCT) patients with therapy-refractory chronic wounds were examined over a maximum of twelve weeks. Groups 1 and 2 were treated with CAP once and twice a week, respectively. Patients in Group 3 received placebo therapy once a week.

Results: Wound area decreased significantly by 63.0 % in Group 1 (n = 14, P = 0.005) and by 46.8 % in Group 2 (n = 13, P = 0.007). In Group 3 (n = 10) the wounds grew on average 17.5 % larger. A significant reduction in pain was measured in both CAP-treated groups (Group 1: P = 0.042; Group 2: P = 0.027). Only in Group 2 was there a significant improvement in wound-specific quality of life (P = 0.005). After the 12-week CAP treatment, the reduction in bacterial load compared to the day of study inclusion averaged 50.4 % for Group 1 and 35.0 % for Group 2.

Conclusions: Our RCT shows that treatment with CAP improves various aspects of wound healing in patients with therapy-refractory chronic wounds. The results obtained for once weekly treatment with CAP were not inferior to those obtained when CAP treatment was three times a week. Treatment once a week is also easier and more economical to implement in clinical routine.
A central, important aspect of our pilot study was therefore to determine whether once-weekly application of CAP in patients with chronic wounds could achieve comparably beneficial results to those obtained with three treatments a week. In addition to a reduction in the size of the wound, the objective was to examine other aspects relevant to the patient, such as wound-specific quality of life, antimicrobial effectiveness and pain relief achieved through CAP treatment.

Patients, material and methods

Trial design

Patients for this prospective, randomized clinical trial (RCT) were recruited through the outpatient wound center at the Department of Dermatology of Essen University Medical Center. The trial comprised adults with chronic wounds that had persisted for at least eight weeks with no tendency to heal despite ostensibly the best possible treatment [11].

Patients with wounds that could not be debrided due, for example, to tenderness and/or too little necrotic wound debris, patients undergoing systemic antibiotic treatment or those where such treatment was not completed 14 days prior to the beginning of the trial, patients undergoing topical antimicrobial treatment, gestating patients, breast-feeding patients and cognitively impaired patients were all excluded from the trial. The Ethics Commission voted in favor of carrying out this study.

Methods

Cold atmospheric plasma was generated using the SteriPlas® device manufactured by Adtec, Hounslow, UK (Figure 1). The treatment head contains ionization chambers that use electrodes to bombard argon gas with electrons and to accelerate the resulting plasma ions via an electric grid. Three dimensional wound measurement was performed using the Silhouette® camera system (ARANZ Medical, Christchurch, New Zealand), which deploys three lasers to measure the wound, thus calculating the length, width, circumference, area, depth and volume (Figure 2). A MolecuLight i:X® device (MolecuLight, Toronto, Canada) was used to record conventional (Figure 2) and autofluorescence wound images (Figure 2) of bacteria in real time. Semiquantitative swabs using the Essen Rotary technique were applied to determine the bacterial colonization of the wound, and results were evaluated at the Department of Microbiology of Essen University Medical Center [12]. For more extensive bacteriological procedures, debris was processed with crystal violet/iodine Gram staining at Jena University Medical Center. Calculation of the percentage of samples contaminated with bacteria was performed using the ImageJ® software (Wayne Rasband, National Institutes of Health, Bethesda, USA). Patients completed the Wound-QoL questionnaire once weekly prior to commencement of treatment with a view to assessing the wound-specific quality of life [13].

The primary target criterion was to reduce the area of the wound. Secondary target criteria were reduction of the bacterial load within the wounds, reduction of wound depth, pain relief and improved wound-specific quality of life.

Treatment procedure

One each of conventional and fluorescent images were taken during every consultation after undressing the wound. This was followed by 3D measurement of the wound before a semiquantitative, bacteriological swab was taken. Mechanical wound debridement was performed once a week using a ring curette (Stiefel, Munich, Germany) and sterile compresses. Wound flushing was carried out exclusively using physiological saline solution. The collected debris was filled...
into transport containers with 4% formaldehyde solution. Once a week, prior to commencement of treatment, the pain level was rated by means of a visual analog scale (VAS) and the wound-specific quality of life was assessed using the Wound-QoL.

The CAP treatment took two minutes for each application area. Thereafter, a conventional and a fluorescence image were again taken, followed by a new bacteriological swab. No antimicrobial wound products were permitted as dressings. The wounds were treated exclusively with hydrogel (Suprasorb G, Lohmann & Rauscher, Neuwied, Germany) and/or greased gauze (Adaptic, Systegenix, Wiesbaden, Germany). Patients in Group 1 were treated once a week with CAP and those in Group 2 three times a week. For patients in the placebo group (Group 3), all steps taken were identical to those in Group 1. The only difference was that, whereas the plasma device was switched on and thus generated the device’s typical background noise, the argon gas function for generating plasma was not activated. The maximum treatment duration was set at twelve weeks.

Table 1  Description of the patient cohorts.

| Treatment      | Group 1 (1 x/week) | Group 2 (3 x/week) | Group 3 (1 x/week) |
|----------------|---------------------|--------------------|-------------------|
| Number of patients | 14                  | 13                 | 10                |
| Men            | 6                   | 11                 | 5                 |
| Women          | 8                   | 2                  | 5                 |
| Average age (years) | 65.21               | 66.82              | 73.74             |
| Average wound size (cm²) | 11.01               | 14.68              | 3.02              |

Statistical evaluation

Due to the small group sizes and high variance, we selected the non-parametric Wilcoxon rank-sum test for statistical evaluation of the results. SPSS software version 25 (IBM, Armonk, USA) was used.

Results

Patient cohort

The trial comprised a total of 37 patients (15 women and 22 men) with recalcitrant, chronic wounds that were treated (Table 2). The average age was 68 years, the average wound size was 10.1 cm² (Table 1).

Wound size

Therapy resulted in a wound area reduction of 63.0 % for Group 1 and 46.8 % for Group 2. In contrast, the wound size reduction for Group 3 was 46.8 %.
area of the placebo group increased by 17.5 % (Figure 3). The computed parameters and \( P \) values support the results with a high level of significance after twelve weeks of CAP treatment performed either once a week (\( U = -2.830 \), \( P = 0.005 \)) or three times a week (\( U = -2.691 \), \( P = 0.007 \)). This tendency was already apparent after seven weeks. With regard to interpreting the results, attention should, however, be paid to the large variances in the median in week 0 (3.8 cm\(^2\) vs. 12.2 cm\(^2\) vs. 1.6 cm\(^2\)) (Table 3).

At the beginning of the trial, the wound depth averaged 2.4 mm in Group 1, 2.8 mm in Group 2 and 2.6 mm in the placebo group. Over the course of treatment, wound depth was reduced by 53.5 % in Group 1, by 16.6 % in Group 2 and by a significant 34.2 % in the placebo group (\( U = -2.095 \), \( P = 0.036 \)) (Figure 3, Table 3).

### Pain

The 44.9 % reduction in pain in Group 1 was comparable to the 44.2 % in the placebo group. Pain relief in Group 2 was much more significant, at 65.2 %. In Group 1 and Group 2, the pain relief after seven and twelve weeks is statistically significant (\( U = -2.032 \), \( P = 0.042 \) and \( U = -2.207 \), \( P = 0.027 \)). Pain relief in the placebo group does not reach statistical significance (\( U = -1.826 \), \( P = 0.068 \)) (Figure 3, Table 3).

### Wound-specific quality of life

Wound-specific quality of life (Wound-QoL) improved 28.4 % over the treatment period in Group 1, 36.6 % in Group 2 and 29.6 % in the placebo group. Of the three groups, only Group 2 demonstrated a significant Wound-QoL reduction, both after seven (\( U = -2.984 \), \( P = 0.003 \)) and twelve weeks (\( U = -2.806 \), \( P = 0.005 \)) (Figure 3, Table 3).

### Bacteria

In none of the groups was it possible to objectify a significant reduction in bacterial colonization in terms of the number of different types of bacteria in each wound. The average number...
of germ types detected per wound by means of semiquantitative swabs was virtually unchanged between the first and last day of treatment, with 1.1 vs. 1.1 in Group 1, 1.7 vs. 1.8 in Group 2 and 1.5 vs. 1.4 in the placebo group. Furthermore, the semiquantitative swabs over the twelve-week treatment period did not reveal any significant results in terms of the microbial composition of the wound surface in the three groups.

In Group 1, an average reduction in bacterial load of 50.4 % over the full course of the trial was objectified histologically in the debris. For Group 2, this value was 35.0 %. Due to technical problems, it was not possible to evaluate the data of the placebo group.

An in-house evaluation method was developed for the images taken using a MolecuLight® device in order to determine the area colonized by bacteria. Determining the pixel-based RGB gamut values enabled computation of quantitatively comparable values from an image. A total of 15 of the 27 wounds treated with CAP could be successfully evaluated as a preselection had to be made in order to avoid falsification of the values due to reflecting wound surfaces or very bright surfaces. By comparing red stains prior to and after one-off mechanical debridement, which visually illustrates the bacterial settlement, a significant reduction in bacterially colonized areas averaging 76.9 % (U = –2.032, P = 0.042) could be seen immediately after a single treatment with CAP. This value derives from the comparison of wounds after mechanical debridement and wounds that were subsequently treated with CAP, and thus excludes mechanical removal of bacteria as an influencing factor.

Discussion

In recent years, an increasing number of clinical studies have reported on successful CAP treatment of patients with chronic wounds. To date, the focus of such research has been placed on antimicrobial effectiveness [14, 15]. The biological effect of CAP is mediated mainly through generation of ROS, OH radicals, nitrogen compounds, ions, electrons, photons, ozone and UV light. Ozone is employed for disinfection purposes in various areas of medicine. It also has, however, a potentially harmful effect on the respiratory tract and is suspected of increasing the mutation rate [16, 17]. Several studies have therefore examined the potentially harmful effects of CAP [16, 18, 19]. The authors drew different conclusions, indicating health risks or suggesting potentially harmful effects at higher concentrations. These effects depend on the devices used, among other factors. Cold atmospheric plasma can be generated with ambient air or by adding noble gases, such as argon, from external sources. How many potentially harmful substances are created over the longer term during CAP treatment and to what concentrations the operator and patients are exposed when using the device cannot be specified without precise air analyses and should be examined in more detail in the future. Comparable studies with the predecessor model of our device did not describe any relevant side effects among patients or operators [6, 9, 14].

Within the scope of our trial, CAP was easy to apply and the procedure could be performed quickly and pain free. Patients in our trial who were treated with CAP 3 x/week

| Indicator | CAP Baseline (Week 0) | Post CAP (Week 12/Healing) | Indicator | P-value |
|-----------|---------------------|-----------------------------|-----------|---------|
| Wound area (cm²) | 1 x/ week | 3.85 (2.00 / 20.43) | 1.20 (0 / 10.60) | U = –2.830 | 0.005 |
|            | 3 x/ week | 12.20 (2.60 / 20.70) | 4.20 (0.60 / 12.45) | U = –2.691 | 0.007 |
|            | Placebo  | 1.65 (1.00 / 3.93) | 1.75 (0.53 / 6.08) | U = –0.357 | 0.721 |
| Wound depth (mm) | 1 x/ week | 2.00 (1.00 / 3.00) | 2.00 (0.50 / 3.00) | U = –1.552 | 0.121 |
|            | Placebo  | 2.50 (1.00 / 4.00) | 1.00 (0 / 2.00) | U = –2.095 | 0.036 |
| Pain (VAS) | 1 x/ week | 0.50 (0 / 3.50) | 0 (0 / 0.25) | U = –2.032 | 0.042 |
|            | 3 x/ week | 1.00 (0 / 4.00) | 0 (0 / 0.75) | U = –2.207 | 0.027 |
|            | Placebo  | 5.00 (0 / 6.25) | 1.00 (0 / 5.00) | U = –1.826 | 0.068 |
| Wound-QoL | 1 x/ week | 27.00 (17.25 / 48.00) | 19.00 (5.00 / 54.75) | U = –0.724 | 0.469 |
|            | 3 x/ week | 24.00 (12.00 / 32.50) | 9.00 (3.50 / 28.50) | U = –2.806 | 0.005 |
|            | Placebo  | 29.50 (10.00 / 49.00) | 19.50 (4.00 / 50.00) | U = –1.684 | 0.092 |

Abbr.: CAP, cold atmospheric plasma; VAS, visual analog scale; QoL, quality of life
felt the greatest pain relief. If Group 1 is compared with the placebo group, the reduction is on a virtually identical level. It can thus be hypothesized that the pain relief in Group 1 is more likely due to the regular changing of the dressing and wound cleaning by medical specialists. Patients in Group 1 experienced significant pain relief after twelve weeks, which is not found in the placebo group. The considerably greater pain relief in Group 2 may stem from the more frequent dressing changes done by a specialist and/or from the plasma treatment [6, 20].

The Wound-QoL results for Group 1 and the placebo group are likewise not far apart. Neither after seven nor twelve weeks is it possible to detect any statistically significant differences in the results. Group 2 stands out with a 36.6 % reduction in Wound-QoL. Both after seven and twelve weeks of CAP treatment, a significant reduction in Wound-QoL is apparent, translating to an improvement in the wound-specific quality of life. So far, the Wound-QoL has not been performed in any other CAP trials so that no direct comparisons are possible. In principle, it is self-evident that there is a correlation between healing of the wound and an improvement in the quality of life.

The positive effect of CAP on wound area reduction described in several studies was also confirmed in our study. Whereas treatment of the placebo group did not prevent wound area enlargement, the wound areas saw a significant decrease of 63.0 % in Group 1 and of 46.8 % in Group 2. Already after seven weeks, the statistical analysis of Group 1 and Group 2 demonstrated a significant reduction in wound area that continued to improve in both groups until the twelfth week. In this study, treatment with CAP once a week is generally superior to treatment three times a week. It should be mentioned here that the higher weekly CAP dosage could already result in an excessive exposure due to application of ROS and UV radiation, among other factors. To date, only minor cell toxicity and no cell mutagenic effects have been identified following one-off plasma treatments of a two-minute duration [19]. Nevertheless, neither the exact effects nor the long-term effects of CAP are sufficiently understood [21]. A mere 37 patients were examined within the scope of our trial. Despite this low figure, the difference in wound area changes in the three groups is substantial enough to deem the influence of CAP on clinical improvement very probable. In one hypothesis, various proinflammatory cytokines, the expression of which is stimulated by CAP treatment in the wound area, have been suggested as the cause of improved wound healing. For example, one study identified an increase in interleukin (IL)-6 and -8 in wounds treated with CAP. These cytokines may play both a positive and a negative role in wound healing. CC chemokine ligand 2 (CCL2/MCP-1) and Transforming Growth Factor (TGF) β1 and β2, which are involved in inflammatory and wound healing processes, were also found to be elevated [20, 22]. The greatest improvement in wound depth reduction was generally found in Group 1. However, as the wounds were very shallow (2.4 mm in Group 1; 2.8 mm in Group 2; 2.6 mm in the placebo group), this value should rather be seen as unspecific.

In contrast to other publications, no difference in the number of bacterial species could be detected in our study over the course of the investigation. Comparing the average number of bacteria per wound, there is hardly any difference between the three patient cohorts.

The growing number of antimicrobial resistances is an ever-increasing problem worldwide. Within the framework of what is known as the “Antibiotic Stewardship” (ABS), a wide-ranging concept for responsible, targeted use of antibiotics in infectious diseases is consequently described and demanded by policymakers [23] A major benefit of CAP in wound treatment, beside the rapid, contact-free and painless application, is the further reduction in the use of antibiotics [24]. Another study showed that CAP treatment was able to achieve a reduction in bacterial load of up to 40 % in comparison to wound treatment without CAP. This study, however, involved daily treatment with CAP. In addition, the bacterial count was performed using nitrocellulose membrane filters, a type of mechanical debridement. One further important difference arose from the fact that in this study the majority of patients received antibiotic treatment [9], while our study design strictly dispensed with all kinds of antimicrobial treatment [25–27]. However, evaluating the gram staining in the debris also showed a reduction in bacterial load of 50.4 % in Group 1 and 35.0 % in Group 2 in our study. These results confirm a significant reduction in bacterial populations through CAP treatment and are more accurate than evaluation of the semiqualitative swabs. In the case of the findings that could be evaluated with MolecuLight®, a significant reduction of 76.9 % of the areas populated by bacteria was also found in patients treated with CAP.

A meta-analysis performed in 2018 analyzed studies on the use of CAP for safety and effectiveness in reducing bacterial load and wound area [10]. A total of 93 RCTs were found. Of these, nine studies with finalized publications, exact documentation and figures of the outcomes and a comparison of treatment with or without CAP, were included in the final analysis. With regard to the healing of chronic wounds, four studies with a total of 148 versus 148 patients were compared. No significant benefit from CAP with regard to different wound healing was found compared to the control groups. Five studies with a total of 91 vs. 79 patients were compared with regard to the reduction in bacterial load. Here, again, there were no significant benefits from CAP. This meta-analysis revealed a number of problems in a direct comparison.
of various CAP studies. The number of patients in the studies was rather small with between eight and 73 patients, and the measuring techniques were not uniform. Determining wound size and bacterial load is, however, subject to many factors that can have a strong impact on the results. Other important differences were the CAP devices used, the types of application and the different application times. This shows that, despite encouraging results, it is currently not possible to make a clear recommendation regarding treatment intervals, intensities or treatment duration.

Limitations

A critical aspect of our study is the very heterogeneous patient cohort. However, all patients had in common the fact they suffered from a recalcitrant chronic wound. The small number of patients in each group, a difference in the average age of up to seven years, the difference in the average wound sizes and mixed entities could have an additional influence on the study findings. The results of this study may nevertheless be useful in the planning of further, ideally multicentric, RCTs.

Conclusion

Our RCT clearly shows that treatment with CAP improves, in comparison to placebo, various parameters of wound healing in patients with chronic wounds. In this respect, the results achieved with application once a week were not inferior to those achieved with application three times a week. Treatment once a week is easier to integrate into the daily clinical routine and, among other things, provides time management and cost benefits.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Correction added on October 5, 2020, after first online publication: Projekt DEAL funding statement has been added.

Conflicts of interest

Maurice Moelleken received travel expenses from AdTec. Finja Jockenhöfer did not receive any financial support for lectures, consultations and/or studies. Cornelia Wiegand received financial support for lectures, consultations and/or studies from the following businesses: B. Braun, Coloplast, Convatec, Hartmann, Lohmann & Rauscher, SastoMed, Urgo.

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