Use of Cold Atmospheric Plasma (CAP) in the Treatment of Chronic Wounds

This literature review shows its potential.

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Introduction of Cold Atmospheric Plasma (CAP)

Irving Langmuir first described plasma in the 1920s as an ionized gas.[1,2] Plasma is created when thermal energy is applied to an atom to free valence electrons from atomic orbit. Electrons require less external energy to 'heat up' or excite since their mass is 1836 times less than that of the heavy particles (protons and neutrons).[3] Thus, when external energy is applied to the atom, the electrons will excite before the heavy particles in the middle. Thermal plasma occurs when both electrons and heavy particles are excited and are at equal temperatures. Non-thermal plasma or non-equilibrium plasma occurs when the electrons are 'hot' while the heavy particles remain 'cold'.

Non-thermal plasma, also known as cold atmospheric plasma (CAP), operates at room temperature (24°C to 30°C), allowing for direct contact with wounds without thermal damage to healthy tissue,[1,4] a significant advantage.

While thermal plasma has been studied for its ability to sterilize and cauterize, its high temperature can cause thermal damage to tissues. Non-thermal plasma, also known as cold atmospheric plasma (CAP), operates at room temperature (24°C to 30°C), allowing for direct contact with wounds without thermal damage to healthy tissue,[1,4] a significant advantage. Recent research on CAP has revealed promising applications for burns, cancer, and wound care.[5]

Amputation is an unfortunate consequence of unaddressed surface biofilms in diabetic patients with chronic wounds. Delayed wound closure due in large part to the lack of sensation allowing diabetics to ambulate on open wounds prolongs environmental exposure which increases the risk of infection and spread to deeper tissues. Even after amputation, these diabetic patients have a dismal five-year survival rate of 30.6%.[6] Infection of diabetic foot ulcers is also a result of a decreased immune response and lack of both macro and micro vascular flow. Thus, there is a demand for a treatment which can promote healing rates, decrease risk of infections, and ultimately provide a strong deterrent to delayed healing and possible amputation. CAP, although a technology in its infancy in wound healing, may help to fill that need.

Direct CAP application is painless to the subject and is easily applied to the targeted area. It has a "purple lightning" appearance that "shocks" the skin multiple times per second, but is imperceptible to the patient. Overall, the ease of application and quality of CAP treatments make a great argument for its integration into mainstream wound care. Figure one demonstrates a CAP application to the plantar first MTPJ and tip of the distal phalanx using a dielectric barrier discharge device (Figure 1A and B).

Analysis of CAP's Effects on the Stages of Wound Healing

Hemostasis

Hemostasis occurs when fibrinogen is cleaved by thrombin, producing fibrin that amalgamates to create a mesh-like clot. Normally, doctors speed up the clotting process by adding thermal energy or direct pressure to the wound, both of which can create excess strain on the wound and surrounding tissues. The longer the wound

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New Concepts and Studies

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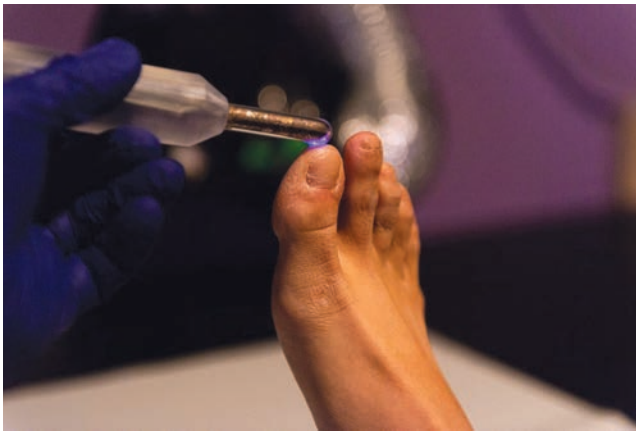

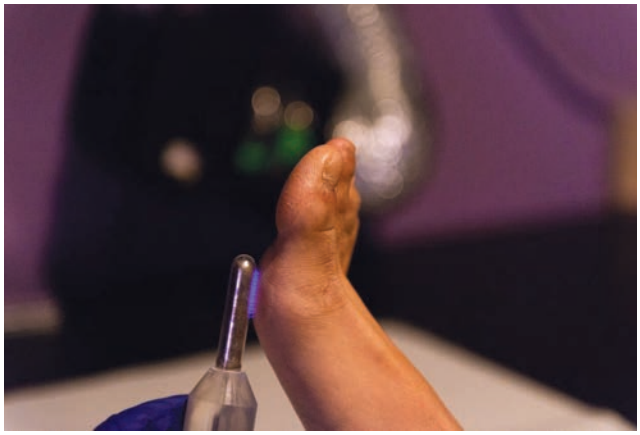

Figure 1A & B: Utilization of CAP on the distal hallux 1a and first MPJ 1b *(Courtesy of aaplasma)*

is actively bleeding, the greater the loss of blood and the risk for infection, thus demonstrating a need to accelerate blood coagulation. In an in vitro study, CAP increased the conversion of fibrinogen into fibrin, which sped up clot formation during wound treatment.[7] Fridman, et al. further support the ability of CAP to decrease bleeding. CAP was able to reduce clotting time of blood droplets from 15 minutes to less than one minute post-treatment.[8] Furthermore, a half-minute treatment using CAP prevented hemorrhaging of a human spleen by promoting granulation tissue formation.[8]

Inflammation

Almost all wounds that become chronic are 'stuck' in the inflammatory phase.[9] In general, repetitive trauma, excess bio-load, and decreased vascular circulation will extend this phase indefinitely. Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus (MRSA) are the most prevalent bacteria, found in 23.3% and 14.8% of all ulcers.[10] Bacterial infection is a significant risk factor in creating chronic wounds.[11] CAP was able to successfully decrease three strains of MRSA and four strains of Pseudomonas by 9 logs10 after 10 and 30-minute treatments, respectively.[10] CAP has demonstrated anti-bacterial properties as it has been found to reduce other common wound bacteria such as Corynebacterium spp, Klebsiella (pneumoniae ssp.), Proteus (mirabilis and vulgaris), Streptococci (A&B), and E. coli.[10] By ensuring proper chronic wound bed hygiene, a progression of infection, a reduction in healing time, and a lower incidence of complication should be realized.

Chronic diabetes and high blood sugar decrease the healing rate by affecting the microvasculature as well. Formation of new blood vessels must be promoted to overcome this disadvantage. Kisch demonstrated that CAP-generated ROS positively influenced angiogenesis.[12] By treating the wound for 90 seconds for three sessions, blood flow and oxygenation was increased by 28%, 45% and 47% ($p < 0.05$). This demonstrates that CAP can improve the microvasculature, especially when applied repeatedly.[12] In conclusion, not only will patients with diabetic foot ulcers benefit from CAP treatment, those with burns and other skin conditions resulting from excessive inflammatory responses might benefit as well.

Proliferation

The proliferative phase is the third phase of wound healing, it is characterized by the creation of new viable tissue, and the re-epithelization of the ulcer. Needless to say, the faster the ulcer heals, the less chances there are for further infection. Experiments conducted both in vitro and in vivo demonstrated growth factors, such as Il-6, MCP-1, TGF-B1/B2, alpha-SMA, and collagen type I, increasing after CAP exposure ($p < 0.05$).[13] The increase in these growth factors all point to the idea that CAP is beneficial to various natural pathways of regeneration such as up-regulation of immune processes and fibroblast migration. The mechanical strength of CAP-repaired tissue was significantly higher than that of the control group as well ($p < 0.05$).[14] Chatraie, et al. further support the growth factor hypothesis as they found CAP demonstrated a measurable increase in wound re-epithelialization, angiogenesis, and collagen synthesis compared to the control.[14]

There is also evidence to suggest that the application of CAP can further stimulate osteocyte, chondrocyte, and myocyte differentiation in vitro.[15,16] In summary, CAP has the advantage of increasing growth factors over standard

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treatments including, but not limited to, dry sterile dressings, debridement, and antibiotics.

Clinical Trials

The benefits of CAP can be seen outside the lab as well. Various case studies have also demonstrated success in clinical trials. Mirpour, et al. report CAP-treated wounds decreased by 77% compared to the standard of care group, which achieved only a 36% reduction after three weeks.[17] Furthermore, another study done by Dr. Stratmann to compare CAP treatment to placebo found an overall decrease of base wound size of 69.5% (CAP) and 44.8% (placebo).[18] These clinical trials support the hypothesis that CAP outperforms the normal standard of care by decreasing wound size at a faster rate in a clinical setting.

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Concluding Remarks

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Overall, this review demonstrates the need for further development of plasma technologies regarding chronic wound care. By effectively utilizing CAP, we hope that this new field can be incorporated into our normal standard of care to increase healing rates and decrease complications with chronic wounds. CAP synergism with existing treatment methods such as hyperbaric oxygen, biofilm-based wound care, NPWT, and skin grafts should also be considered as well.

CAP has great potential in the treatment of diabetic foot ulcers, as CAP is unique in its ability to benefit multiple stages of wound healing without significant risk to viable tissue. Future experiments should focus further on the mechanisms and effectiveness of CAP as well as look at any negative CAP-related long-term effects of which we are not currently aware. **PM**

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Haoning Hu is a fourth year student at Temple University School of Podiatric Medicine. He became interested in Cold Atmospheric Plasma (CAP) after studying its applications on cancer. He decided to continue his interest in CAP after learning that it can be applied to podiatry, particularly diabetic foot ulcers. He is hoping to continue his research of CAP during residency and beyond.