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

This literature review shows its potential.

BY JAMES McGUIRE, DPM, AND HAONING HU

Introduction of Cold Atmospheric Plasma (CAP)

Irving Langmuir first described plasma in the 1920s as an ionized gas. 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). 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’.

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, a significant advantage.

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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 continues healing, the more likely it is to become infected. 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).

Amputation is an unfortunate consequence of undressed 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%. 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.

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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. 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. Furthermore, a half-minute treatment using CAP prevented hemorrhaging of a human spleen by promoting granulation tissue formation.

**Inflammation**

Almost all wounds that become chronic are ‘stuck’ in the inflammatory phase. 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. Bacterial infection is a significant risk factor in creating chronic wounds. CAP was able to successfully decrease three strains of MRSA and four strains of Pseudomonas by 9 logs after 10 and 30-minute treatments, respectively. 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. 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. 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. 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). 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). 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.

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

Concluding Remarks
CAP has strongly demonstrated its ability to disinfect tissue, promote growth factors, improve blood flow, and result in greater wound closure compared to standard treatments.

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Dr. McGuire has been a Clinical Professor at the Temple University School of Podiatric Medicine for the past 27 years. He also serves as director of the Foot and Ankle Institute’s Leonard Abrams Center for Advanced Wound Healing where he has worked since 1999. He has been a founding member of the APWH, the APWCA, and the Council for Medical Education and Testing. He is very involved with several active research trials and numerous papers in the area of wound healing, off-loading, diabetic foot care, and biomechanics of the foot and ankle.

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.