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The feasibility of cold atmospheric plasma in the treatment of complicated wounds in cranio-maxillo-facial surgery

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ABSTRACT

Background: Compromised wound healing in cranio-maxillo-facial surgery is a threat to the patient's rehabilitation. Therapy of chronic and/or infected wounds is time- and cost-consuming, burdensome and occasionally futile. Cold atmospheric plasma is a new approach that promises to overcome these limitations. The aim of this proof-of-concept study was to evaluate the clinical outcome of cold plasma irradiation in patients with impaired wound healing who are refractory to conservative wound therapy and/or revision surgery.

Materials and methods: We enrolled six patients (mean age: 63.5 years; SD 8.8 years; 1 female and 5 males) who experienced various cranio-maxillo-facial surgical procedures and suffered from wound healing disturbances. In addition to established wound care, all wounds were irradiated with cold atmospheric plasma. The primary outcome variable was the attainment of complete wound closure.

Results: In all patients, complete remission in terms of wound closure was observed within a mean time of 15.5 weeks (range: 4–38 weeks). No undesirable side effects were observed, and no inflammation or infection occurred after cold plasma initiation.

Conclusion: The use of cold atmospheric plasma might offer a reliable, conservative treatment option in complicated wound healing disturbances in cranio-maxillo-facial surgery.

1. Introduction

The broad range of surgical techniques regarding tumor resection and reconstruction in cranio-maxillo-facial (CMF) surgery patients generates surgical wounds with different types of localization and underlying pathophysiology. On one hand, clinicians have to deal with wounds of the head and neck region; on the other hand, they face donor site wounds from different regions (e.g., torso and extremities) after harvesting free flaps, mainly the radial forearm or the fibula flap.

Wound healing disorders are a constant threat that are increasing in number, due to the rising age and consecutive comorbidities of patients (Grammatica et al., 2015; Hwang et al., 2016; Suh et al., 2004). Several systemic conditions including diabetes (Ahmed and Antonsen, 2016; Baltzis et al., 2014), chronic alcohol abuse (Anderson and Hamm, 2014), infection with human immunodeficiency virus (Hájek et al., 2009; McMeeking et al., 2014; Nagoba et al., 2014) or medication with immunosuppressants or even chemotherapeutics (Franz et al., 2007; Wagner et al., 2008) potentially impede wound healing. Local factors contributing to healing disorders are microbial infections and locoregional radiotherapy. The impact of radiation on wound healing physiology is dependent on the overall dosage and fractionation regimen (Koerdt et al., 2015; Straub et al., 2015). Several side effects are associated with radiotherapy such as skin atrophy, fibrosis, scarring, wound dehiscence and skin necrosis (Dormand et al., 2005; Gieringer et al., 2011; Haubner et al., 2012).

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Moreover, postoperative wound infection is often caused by bacterial overload. Several studies indicate that a bacterial load of more than 10^5 organisms per gram of tissue can cause wound infection (Franz et al., 2007; Rahim et al., 2016), and chronic wounds are frequently contaminated with biofilms containing multi-resistant species (Georgescu et al., 2016; Serra et al., 2015).

The armamentarium in the treatment of wound healing disorders includes topical anti-infective agents and the use of classic and/or modern (bio-) materials (Canadian Agency for Drugs and Technologies in Health, 2013; Maessen-Visch and van Montfrans, 2016; Pereira and Bártolo, 2016; Salamone et al., 2016), negative wound pressure therapy (Nie and Yue, 2016; Webster et al., 2014) and red and near-infrared light (Rathnakar et al., 2016; Yadav and Gupta, 2016), as well as low-level laser therapy (Fernandes et al., 2016; Mathur et al., 2016) and, last but not least, surgical revision.

Cold atmospheric plasma (CAP) is a new treatment option in wound therapy. Plasma is defined as the fourth state of aggregation next to solid, liquid and gaseous. It is an ionized gas with different components such as ions and electrons, visible light, electrical fields, ultraviolet radiation, thermal emissions and bioactive molecules (reactive oxygen and nitrogen species). CAP has shown promising results in experimental (Fathollah et al., 2016; Hoentsch et al., 2012) and clinical (Isbary et al., 2012; Klebes et al., 2014) studies concerning stimulation of the wound healing complex so far. However, as bacterial contamination of the wound is an important factor impeding the healing process, the antimicrobial effects of CAP, which have even been observed in multi-drug–resistant species, offer synergistic effects in modern wound treatment regimens (Haertel et al., 2014).

The objective of this proof-of-concept study was to evaluate CAP as an additional conservative treatment option in chronic wounds of the surgical and donor site after CMF surgery. It was hypothesized that repeated application of CAP to the wounds every 7 days would lead to complete wound closure and absence of infection.

2. Materials and methods

The investigators designed and implemented a prospective proof-of-concept study.

2.1. Compliance with ethical standards

All procedures including assessing data from human subjects were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments (WMA 2013). Approval was granted by the ethical review committee of the Charité–Universitätsmedizin Berlin (EA4/174/15). All patients gave written informed consent before inclusion in the study. Only data assessed at the Department of Oral and Maxillofacial Surgery, Charité–Universitätsmedizin Berlin were included.

2.2. Patient recruitment

Patients suffering from wound healing disturbances after maxillo-facial surgical procedures leading to wounds that were refractory to revision surgery were eligible and were offered CAP treatment. All 6 subjects gave informed consent in written format after 24 h and were included in the study. Recruitment, treatment and follow-up of all patients were performed at the Department of Oral and Maxillofacial Surgery, Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin between March 2015 and December 2016.

2.3. Inclusion, exclusion and drop-out criteria

Patients suffering from a wound healing disorder after CMF surgery were enrolled. The ability (linguistically, physically and mentally) to understand the nature of the study and to participate was necessary. No special exclusion criteria besides the

Fig. 1. (a, b) Chronic wound healing disorder of the donor site after harvesting of a free fibula osteoseptocutaneous flap (overview and detail). The wound was infected with *Pseudomonas aeruginosa* and did not heal for 15 weeks post-surgery. (c) Wound closure after 8 weeks of cold atmospheric plasma treatment.