Chapter 8
Clinical Studies on Cold Gas Plasma Applications: The Autonomous Patient and Getting Informed Consent for Treatment and Clinical Studies

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8.1 Background

This chapter is spreading the official Clinical Practice Guidelines (Leitlinien) of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) concerning Rational Therapeutic Use of Cold Physical Plasma (Rationaler therapeutischer Einsatz von kaltem physikalischem Plasma), AWMF 007-107, 23/Feb/2022. The intention of the chapter is to utilize for study purposes, especially for patient recruitment, the official template for medical briefing of patients as an obligatory part of an informed consent document.

The patient targeted briefing part is a complete citation of the official guidelines.[1] The footnotes are the new content, targeted scientific information for the doctor to be prepared for the patient consultation. This combination of official guidelines at the hands of a patient and scientific comments at the hands of a doctor is needed to support the recruitment of study patients for clinical research in plasma medicine.

[1] Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG) Rationaler therapeutischer Einsatz von kaltem physikalischem Plasma Version 1.0 vom 23. Februar 2022: https://www.awmf.org/leitlinien/detail/ll/053-054.html. Editor Hans-Robert Metelmann. Access 22/08/2022.

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8.2 Template

Dear Patient,

You are consulting your doctor because of a medical or aesthetical problem, and you will probably participate in a clinical study. The key term plasma medicine has been mentioned. It became obvious to you, that plasma medicine has nothing to do with blood plasma. Now, you are interested to learn about plasma medicine, and why it makes sense to consider it for treating your problem.

The purpose of this document is to make you familiar with the basic clinical principles of plasma medicine. Please read this information carefully. Your doctor will inform you about treatment options with plasma medicine, typical risks and possible consequences, and the details of the medical intervention regarding your case. When you feel adequately informed and expressly wish to undergo plasma medicine treatment, please confirm your consent with your signature.

8.2.1 General Aspects of Plasma Medicine

Colloquially, the term "plasma medicine" often refers to tools that generate physical plasma or to products activated by physical plasma, mainly used for cosmetic purposes and by laypersons. Your doctor, on the other hand, is talking about cold physical atmospheric pressure plasma, abbreviated to cold plasma or CAP, generated by officially approved medical devices, and indicated with particular relevance for the medical therapy of chronic wounds and infected skin.

If you suffer from a severe skin infection or wound that is not healing, you have experienced the heavy burden on your health and well-being. These problems can sometimes be difficult to handle by established therapeutic procedures, calling for innovative treatment like CAP medicine.

A wound by itself is not a disease, and wound healing is just a natural process that does not require a targeted treatment. However, problems may arise

- when open wounds become severely infected by pathogens,
- when wound healing is retarded and the risk of infection is rapidly increasing,
- when wounds cannot heal because of consuming illness and show massive infection,
- when pain requires rapid healing of open wounds or infected skin,
- when general risk prevention requires rapid healing of open wounds or infected skin,
- when wounds and skin infections are health-threatening suppurative focuses, or
- when infected wounds contaminated with certain bacteria are causing smell and odor.

CAP medicine is covering all of these indications.

You might be interested to learn that CAP is ionized gas, generated by physical energy. CAP induces biochemical reactions and releases molecules that interact with human wound cells and with microbial cells, such as infectious bacteria and viruses. CAP therefore accelerates wound healing in two ways: by killing harmful germs at the wound surface (antisepsis) and by promoting the growth of healing cells (tissue regeneration and microcirculation). This double effect is a unique advantage of CAP treatment compared to conventional and established wound care measures.

CAP may look like bluish little flames, but with a temperature not higher than 40 °C, it works on the cells without causing thermal damage, ensuring a painless treatment.

Moreover, CAP application is a touch-free treatment that avoids unpleasant contact of the device with your wound or irritated skin and prevents the risk of unintentionally injuring numb wounds.

8.2.2 Selection of Patients

You have learned that CAP treatment is useful for you, in case you are suffering from problematic wounds or infected skin and mucosa. This includes patients with

- chronic and infected wounds,
- wounds with standstill of healing but without infection,
- skin and mucosa lesions at risk of serious progression,
- non-healing wounds by other reasons,
- skin and mucosa with certain local infections and purulent focuses.

Patients suffering from infective and inflammatory skin and mucosa diseases like herpes zoster, atopic eczema, (oral) lichen planus or acne also benefit from CAP application.

You may also belong to a group of patients considered at risk of poor wound healing, who benefit from CAP treatment as preventive measure. This includes patients

- with wounds that are not closing within 28 days,
- aged 60 years or older,
- after the menopause,
- under systemic steroid medication
- taking medications that inhibit wound healing (e.g. glucocorticoids, immunosuppressants, NSAID) or
- with cancer or a history of previous impaired wound healing.

You see that cold plasma application can be used to support the healing of lesions and acute surgical wounds in cases, where the patient's difficult health-status, biographic condition or medication push the risk of problematic wounds. Accelerating the wound healing can also help to reduce scar formation. Together with the

potential to prevent wound infection, CAP treatment is a promising option to control the risk of surgical site infections in the field of plastic surgery and aesthetic medicine.

8.2.3 Choice of Plasma Devices

Your individual medical problem calls for individual treatment, and your doctor will propose and choose the most appropriate cold plasma device for your treatment task. You might be interested to learn that there are two types of medical devices in use, approved by the competent authorities since 2013.

One type is called jet plasma device: CAP is generated by electrical tension within a slim tubular handpiece. The resulting ionized gas is driven out by a propellant gas and looks like a jet flame. This "plasma cocktail" consists of atmospheric air, noble gases (argon, helium) and gas mixtures of the working gases.

The other type of medical device is based upon dielectric barrier discharges (DBD): CAP is generated within an electric field forming between the large surface of a flat handpiece and the surface of the skin. This "plasma cocktail" looks like a carpet and consists of atmospheric air.

Jet plasma devices with plasma flames shaped like the tip of a lancet are very suitable for precise interventional procedures under visual inspection. They are used on wound craters and rugged tissue, on regions with undercut, and for intraoral application. DBD plasma devices with plasma carpets are very convenient for the quick treatment of large and flat wounds and infected skin areas.

Rest assured that your doctor is only using CAP devices with CE certification as medical devices class IIa according to the European Council Directive 93/42/EEC. These devices work with plasma sources that have been extensively examined for their biological and physical properties and have been tested in detailed preclinical and clinical investigations.

8.2.4 Handling of Complications

You might have experienced that standard treatment of wounds and skin infections does not succeed in some cases. This is also true for cold plasma therapy. Even with well proven healing effectiveness of CAP medicine, there are some patients with insufficient treatment results. Especially in chronic wounds, plasma medicine plays an important role—but it is not the only player. Continuous debridement, proper wound dressings, and keeping relevant co-morbidities and current medication under control are important as well.

First CAP medical devices have been approved in 2013 and still there are no known serious side effects or complications of therapy. Any enhanced risk of genotoxic and mutagenic effects of CAP treatment has been excluded by well-established in vitro tests as well as by a long-term animal trial and long-term clinical observations.

In principle, complications in medical procedures are due to the general health and medical condition of the patient. Please help your doctor to identify any risk of complications by carefully reporting your health status and medical history.

8.2.5 Frequently Asked Questions

Dear Patient,

To sum up this information supported by scientific data, we would like to answer some of the frequently asked questions. (The footnotes might provide your doctor with scientific additional background information in case you will ask for more detailed medical consultation.)

1. Might cold plasma application be effective in my case?

Yes, we recommend the application of cold atmospheric pressure plasma for the curative treatment of chronic and infected wounds or prevention of surgical site infections.Randomized clinical studies and reviews have confirmed the effectiveness in decontamination and tissue regeneration even for prevention and in skin diseases caused by multidrug-resistant organisms.[2]

We suggest the palliative treatment of ulcerated, open, anaerobically contaminated tumor metastases with cold atmospheric pressure plasma as a measure of germ reduction to mitigate odor development and pain.[3]

If necessary, the treatment should be supplemented by appropriate wound debridement and by specialist care for relevant comorbidities.

2. How is plasma medicine working?

Medical cold plasma devices generate an ionized gas, visible as a tiny blue light with body temperature. The main active components of this plasma are reactive nitrogen and oxygen species (RNS, ROS), UV radiation and electric fields.[4] The ionized gas directed towards the medical target area will induce proliferation of relevant wound cells, stimulate blood perfusion of the compromised tissue and reduce significantly contamination and infection with pathogens.[5]

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[2] This recommendation is based upon randomized clinical studies of cold atmospheric pressure plasma for the curative treatment of chronic and infected wounds [12, 68, 69, 89] and current expert consensus of 14 scientific medical societies in Germany actively involved in cold plasma medicine.

[3] This suggestion is based upon several pilot studies, case reports and clinical experience [67, 84].

[4] Certified plasma sources either generate a fine beam plasma (jet concept), or emit a flat, carpet-like plasma (Dielectric Barrier Discharge, DBD) [7, 13, 26–28, 42, 53, 73, 92, 93, 95, 100, 101, 105, 106]. Plasma jets are particularly suitable for precise application of plasma directed under visual control and without touch of the wound or tumor, and for treating deep wound craters, fistulas, and undercuts. DBD-devices are well suited for use on large, flat treatment areas. The composition of cold atmospheric pressure plasma depends on the source design and variables such as room air, humidity, and skin surface.

[5] Plasma devices are approved for treating delayed wound healing and microbially contaminated wound and tumor surfaces, skin, and mucous membranes [12, 15–17, 19, 20, 22, 29, 30, 33, 34, 36,

3. Is plasma medicine safe?

Yes, there are no scientific reports of carcinogenic, genotoxic, or mutagenic effects linked to the application of cold atmospheric pressure plasma.[6] Since plasma treatment is local and limited in time, the risk of side effects associated with the entry of ROS and RNS into the tissue is assumed to be extremely low under normal conditions.

4. Are plasma medical devices approved?

Your doctor is using an approved medical device, belonging to a number of plasma sources with comprehensive physical and biological characterization and detailed preclinical and clinical investigations to prove efficacy.[7]

This statement does not include several other plasma tools on the market that claim to be suitable for "plasma medicine" but have no or very inadequate physical, technical, biological, or clinical references to prove this.[8]

5. How is the risk of local or systemic side effects and complications?

Approved plasma devices are in clinical use since 2013. There are no case observations or clinical studies in the literature that report severe side effects of any kind, including carcinogenesis or genetic damage. Cold atmospheric pressure plasma has no clinically discernible thermal effect because, when applied correctly, it barely exceeds the skin temperature of the target area. Slight local effects have to be considered, such as minor pinprick or irritation related to the tip of the plasma plume when using plasma jets. In very rare cases and unclear connection, a brief and mild redness of the skin following unintended touch might occur.

6. Can cold plasma cause cancer?

In many laboratory and animal experiments, physical plasma was examined for a possible induction of cancer. Although natural damage to the DNA could be shown

38–40, 43, 44, 51, 52, 60, 65, 67–69, 74, 77, 81, 84, 89, 97]. Randomized clinical studies[12, 68, 69, 89] and reviews [6, 55, 88] have confirmed the effectiveness, even for skin diseases caused by multidrug-resistant organisms.

[6] The absence of mutagenic effects on mammalian cells has been demonstrated by means of established standard test methods [5, 11, 61, 107], in a long-term animal study [83], and in long-term clinical observations[66, 82]. The UV exposure associated with the use of cold atmospheric pressure plasma is well below the general limit values for personal and occupational safety [4, 14, 59, 76].

[7] The application for treatment purposes is authorized by CE certification as medical devices class-IIa according to the European Council Directive 93/42/EEC. These devices are approved for the treatment of chronic wounds and pathogen associated skin diseases. The approval is based on a comprehensive physical and biological characterization as well as detailed preclinical and clinical examinations [4, 35, 56, 62, 79, 85, 96, 103].

[8] Advances in clinical plasma medicine and its increasing visibility in the media gave rise to dubious providers who advertise devices and corresponding therapies under the name of plasma medicine. Only certified plasma devices whose effectiveness has been confirmed by scientific studies and expert consensus should be used in clinical plasma medicine.

in some cell experiments, cancer induction could not be demonstrated neither in animal experiments nor in long-term clinical studies.[9]

7. How is the plasma medicine procedure going on?

The treatment is following a basic standardization with some individual adaptations, and many application parameters are specifically dependent on the respective type of plasma source. We suggest delegating the application of cold atmospheric pressure plasma to a qualified nurse if circumstances permit.[10]

The effectiveness of cold plasma in healing of chronic wounds and treatment of infected skin is well documented. However, there are always a couple of patients without positive treatment results for unknown reasons. Plasma medicine plays an important role in wound healing—but it is not the only player. Steady debridement, proper wound dressings, restoration and perfusion of vessels, lymphatic drainage, and keeping relevant co-morbidities under control are important as well. This is especially true for chronic wounds.

8. Is the medical effect well controllable?

In wound healing the medical effect can easily be controlled by measuring the regain of skin cover and the shrinking of the wound surface. On-going photo documentation is important. Documents will include scale and date and follow the very basic requirements of scientific medical photography.

9. Does it hurt?

Some patients experience mild pain and an increased production of wound drainage.

The ozone odor linked to plasma treatment can be unpleasant for some patients, especially when used intraorally. Depending on the treatment region and duration of the individual application, it can be helpful to use a dental suction device and to ventilate the treatment room well.

When applying cold atmospheric pressure plasma to intraoral lesions, sensitive tooth areas can be covered with a cotton swab to alleviate stinging sensations. When used in the periocular region, the eye should be protected by a cover.

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[9] No serious adverse effects (carcinogenesis or genotoxic and mutagenic effects) associated with the application of cold atmospheric pressure plasma have been reported [3, 5, 9, 11, 18, 31, 32, 41, 47, 54, 57, 58, 61, 66, 82, 83, 98, 107–109].

[10] Prior to application, it can be useful to remove any biofilm from the treatment area. No drying is required since plasma treatment is more effective when moisture-mediated [84, 102]. Due to the largely painless application, local anesthesia or cooling are not necessary during treatment.

Most clinicians have had good experience with an exposure time of 1 min/cm^2. According to the concept of hormesis, shorter applications tend to have a stimulating effect, longer applications tend to inhibit. The therapy plan for wound treatment should include a few applications per week (2–3 x) with a longer break in between (2–3 weeks). A pure antisepsis and decontamination treatment should include several applications in a row (daily for 1 week). The stimulation of tissue regeneration is independent of the antisepsis [89]. Plasma treatment should be supplemented by appropriate wound debridement. and by specialist care for relevant comorbidities. Once the epithelial cover of a wound is closed, the treatment can be completed. No maintenance therapy is necessary. In palliative medicine, the degree of olfactory relief serves as indicator of treatment progress.

10. Will I see a quick medical effect?

Wound healing is never quick. You have to know that it takes stamina by all persons involved and sometimes many weeks of repeated treatment to reach a reasonable result.

11. Can bacteria become resistant when treated by plasma?

One of the significant advantages of plasma medicine compared to other antimicrobial therapies is its effectiveness against multi-resistant skin and wound germs. From the opposite point of view, the development of new resistances when treating germs with plasma has never been described—neither in clinical cases and studies, nor in pre-clinical and basic research.

12. Is there an inhibitory effect on my normal flora?

Jet plasma devices are able to precisely direct the flame to the surface and extension of wounds without significantly touching unaffected skin or normal flora. DBD medical devices with a plasma carpet may have an overlapping field of action affecting skin with normal flora. However, in principle, there are no case reports or pre-clinical and basic research studies mentioning problematic effects on the normal flora in clinical plasma medicine.

13. Could it be done easier? Are there no alternative solutions?

Patients suffering from problematic wounds usually have experience with many alternative but fruitless solutions. The crucial point should therefore not be whether there is a simpler option, but which option is the most effective.

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