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# Randomized placebo-controlled clinical trial showed cold atmospheric argon plasma relieved acute pain and accelerated healing in herpes zoster

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ABSTRACT

Herpes zoster is an acute painful infectious skin condition due to the reactivation of the varicella zoster virus, with increasing incidence in the aging population. Acute pain relief is usually required and post-herpetic neuralgia requiring ongoing analgesia is a well recognised complication.

Argon plasma treatment has demonstrated efficacy in reducing bacterial load in chronic wounds, and possibly stimulating wound healing. In this study, weekday 5 min plasma treatments with the MicroPlaSter ß device was assessed for safety, pain reduction and healing rates of herpes zoster.

37 inpatients with herpes zoster were treated in a prospective randomized placebo-controlled phase II study with either weekday 5 min of cold atmospheric argon plasma (19, active) or with 5 min of argon gas (18, placebo), in addition to a standard treatment regime. Pain was assessed by visual analogue scale before and after active or placebo application. Digital images of lesions were evaluated independently by three blinded clinicians, with regard to vesicles, erythema and general impression.

Analysis revealed a significantly greater ($p < 0.01$) reduction in pain in plasma-treated patients compared to controls over the course of treatment, and a significantly better median reduction immediately after each treatment ($p < 0.05$). Plasma treatment led to more rapid clinical improvement in the first 1–2 days.

Weekday 5 min treatments with cold atmospheric argon plasma was safe, painless and effective, improving initial healing and acute pain in herpes zoster lesions.



## 1. Introduction

Primary infection with the varicella-zoster virus (VZV) results in chickenpox. Reactivation of the latent virus in either cranial-nerve or dorsal-root ganglia leads to the characteristic clinical presentation of herpes zoster (HZ), a unilateral vesicular eruption in the dermatome associated with the sensory nerve (Fig. 1). The global median incidence of zoster is estimated to be 4–4.5 per 1000 person years, a lifetime risk of 30% [1,2]. Incidence and severity increases with increasing age. In persons older than 80 years, the incidence is 12.0 per 1000 years [2].

Antiviral agents shorten the duration of disease and decrease the severity of acute pain but not the risk of postherpetic neuralgia (PHN), defined as pain persisting 4 weeks after healing [3,4]. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the usual first-line analgesics for the acute pain, escalating to tricyclics, anti-convulsants and opioids as clinically indicated [1,5].

Cold atmospheric plasma (CAP) is an innovative technology to treat infections due to a variety of bacteria, fungi and viruses [6,7]. CAPs have been shown to be safe and effective in reducing bacterial carriage in chronic infected wounds [8–10] and acute wounds [11], and may accelerate wound healing [12–14]. In single case reports, cold atmospheric argon plasma treatment has resulted in pain reduction in infected skin conditions [15,16].

*Abbreviations:* CAP, cold atmospheric plasma; HZ, herpes zoster; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; PCR, polymerase chain reaction; PHN, postherpetic neuralgia; PN, peroxynitrite; RONS, reactive oxygen and nitrogen species; SO, superoxide; VZV, varicella-zoster virus

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2212-8166/

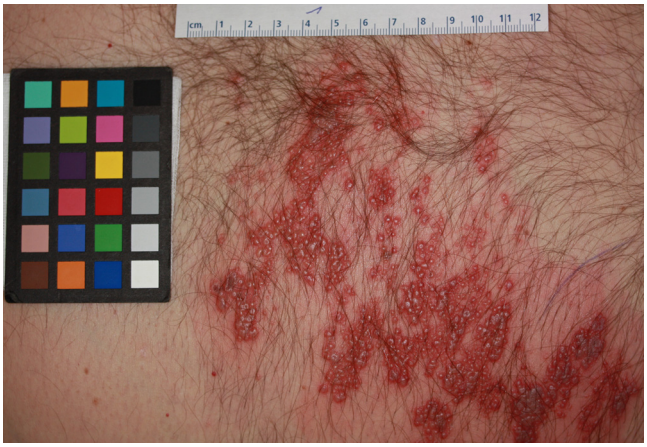

**Fig. 1.** Typical rash of herpes zoster.

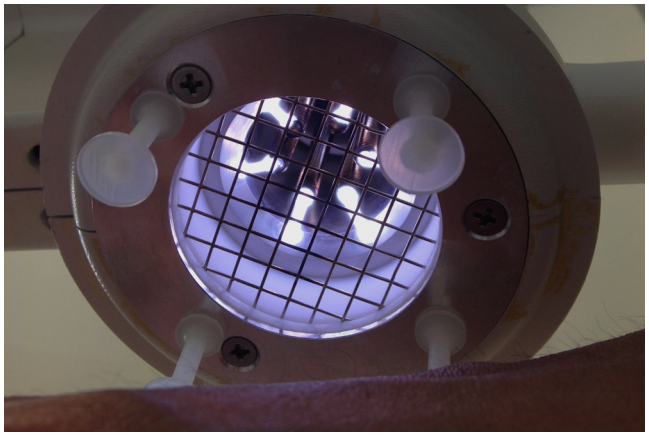

**Fig. 2.** Plasma torch of MicroPlaSter beta.

In this prospective randomized placebo-controlled clinical trial, the effect of weekday 5 min cold atmospheric argon plasma treatments on acute pain and healing was investigated in hospitalised patients with herpes zoster.

## 2. Materials and methods

### 2.1. Patient selection criteria

Patients with HZ admitted to the inpatient hospital wards of the Department of Dermatology, Allergology and Environmental Medicine of Hospital Munich–Schwabing, Germany, or the Department of Dermatology, University Hospital Regensburg, Germany, were invited to participate in the trial, provided treatment for HZ had not started more than 24 h before. Hospital admission was considered for all cases of trigeminal zoster, or where the zoster was severe or painful.

The ethics committee of the Bavarian State Association approved the clinical trial. The trial is in accordance with the Declaration of Helsinki and good clinical practice. All patients signed informed consent forms.

Exclusion criteria were patients under 18 years of age, pregnant and lactating women, patients with dementia, active or metastasizing cancers, or who declined or withdrew consent. Patients with herpetic lesions affecting the eyes and the mouth were not treated, as device safety has not yet been assessed for these sites.

### 2.2. Plasma device and configuration

Active treatment used a microwave driven cold atmospheric plasma device, called MicroPlaSter beta, designed by the Max Planck Institute for Extraterrestrial Physics, Garching, Germany, and manufactured by ADTEC Plasma Technology Co. Ltd., Hiroshima/London. The following settings were used: Microwave frequency 2.45 GHz, Power 80 W; Argon gas flow 5 slm. Distance from HZ lesions to the torch was approximately 2.5 cm. Each exposure was limited by the machine characteristics to a maximum area of 5.6 $cm^2$. Device details have been published [17]. Fig. 2 shows the plasma torch.

The placebo/control treatment involved application of argon gas heated to the same temperature as the plasma. Patients were not able to differentiate between the active and placebo applications.

### 2.3. Treatment protocol

The standard treatment of herpes zoster for all patients was aciclovir iv 5–10 mg per kg body weight per day for at least 5 days, but continued longer if clinically indicated. Treatment commenced on the day of hospital admission. If patients reported pain, treatment with oral paracetamol 500–1500 mg per day was initiated and if necessary combined with long-acting tramadol 100 mg per day. Pregabalin treatment (2 × 75 mg per day) was given for severe pain or extensive disease. Polyhexanide 0.04% gel or cream was applied topically.

In addition to standard herpes zoster care, patients were randomized (computer based random allocation sequence with numbers without any restrictions – *still don't understand this statement – is it required?*) to receive either an application of 5 min cold plasma treatment (active) or heated argon gas (placebo) on weekdays only. A maximum of 4 areas (each up to 5.6 $cm^2$) of zoster lesions were treated in each patient on at least three consecutive days.

The end point was hospital discharge on completion of the iv aciclovir course.

### 2.4. Assessment of pain

Patients were asked to rate their overall pain directly before and after plasma (active) or argon (placebo) treatment using a visual analogue scale (VAS) with a standardized WHO score from 0–10.

### 2.5. Assessment of healing

All treated areas were photographed digitally at each visit and the images were assessed independently by three specialists (two dermatologists and one physician) blinded to the treatment applied. The following features were scored: vesicles, erythema, and overall general impression. Each specialist scored each feature as improvement, deterioration or no change. If all specialists came to the same conclusion, the result was included in the analyses.

### 2.6. Data collection

The following data were collected: Baseline parameters (underlying diseases, allergies, medications, demographic factors), disease characteristics (location, dissemination, number of vesicles/dried vesicles/crusts, and dimensions), treatment received, and pain. Possible side effects (burning sensation, heat, pain) due to plasma or argon application were specifically asked about after each treatment. Quality of life questionnaires (DLQI) were performed at inclusion, on discharge from hospital, and at followup visits.

### 2.7. Treatment endpoints

Plasma/placebo treatment was ceased on discharge from hospital or if the patient elected to stop the treatment. Patients were invited to attend free followup visits two and four weeks after hospital discharge.