

Cold atmospheric plasma for local infection control and subsequent pain reduction in a patient with chronic post-operative ear infection

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Abstract

Following surgery of cholesteatoma, a patient developed a chronic infection of the external auditory canal, including extended-spectrum β -lactamase producing *Escherichia coli*, which caused severe pain. The application of cold atmospheric plasma resulted in a significant reduction in pain and clearance of bacterial carriage, allowing antibiotics and analgesics to be ceased.

Keywords: Cholesteatoma, cold argon plasma, (ESBL+) *E. coli*, external auditory canal, plasma, tissue tolerable plasma

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Research Note

Cold atmospheric plasmas (CAPs) have demonstrated broad bactericidal activity, regardless of the bacterial species and resistance pattern *in vitro* and *in vivo* [1–3]. Plasma is the fourth state of matter and high temperature plasmas have long been used in the sterilization of medical equipment. The development of CAPs now allows application to viable tissue. The efficacy of a CAP device in reducing bacterial carriage and pain

in a patient with chronic nasopharyngeal and external auditory canal infection after cholesteatoma surgery is reported.

A 49-year-old man developed an acquired cholesteatoma of the left tympanic cavity. Cholesteatoma is a rare cyst-like growth formed from keratinizing stratified squamous epithelium in the middle ear cleft or the petrous bone [4]. Surgery is usually required because, although benign, cholesteatoma is destructive and potentially life-threatening [5]. Under antibiotic prophylaxis (amoxicillin combined with clavulanic acid) the patient underwent tympanoplasty, incus resection and reconstructive surgery of the auditory channel. Subsequently, chronic infection developed in the nasopharynx and external auditory canal involving extended-spectrum β -lactamase-producing (ESBL+) *Escherichia coli* and other bacteria (*Proteus mirabilis* and *Enterococcus faecalis*). The infections were accompanied by severe pain, described as severe radiating headaches.

Over the 3 years post-surgery, repeated courses of systemic co-trimoxazole were required in addition to regular wax removal, topical antiseptics (e.g. octenidine) and hydrogen peroxide 0.3% rinses. Aspirin did not relieve the headaches. Co-trimoxazole was taken continuously for the 6 months prior to presentation for CAP treatment.

After informed consent and with ethics committee approval, daily weekday treatment was commenced to both external auditory canals with 5-min cold atmospheric argon plasma (Fig. 1) using the MicroPlaSter β device (built by ADTEC Plasma Technology Co. Ltd., Hiroshima, Japan and London, UK) (Microwave 2.46 GHz, 86 W; Ar 2.2 slm; distance to external auditory meatus 2 cm) [6]. The nasopharynx was not treated as at the time respiratory tract CAP exposure had been investigated only in *ex vivo* models [7].

Plasma treatment was given over 105 days in three blocks of 8, 16 and 19 (total 43) applications, respectively. Pain was recorded using a visual analogue scale (VAS: range 0–10) directly before and immediately after plasma applications. Swabs for bacteriology were taken before, during and after completion of the plasma treatment. Oral co-trimoxazole was continued throughout the initial plasma treatment period, ceasing after the 14th application of plasma. After ceasing the systemic antibiotics, hydrogen peroxide (0.3%) rinsing continued and was performed twice during the final treatment period. No analgesics were required during the treatment period of 105 days. Although the headaches resolved, the patient continued to describe an unpleasant soreness in the ear.

Plasma therapy was well tolerated and no side effects occurred. Immediately after each plasma application there was a mean pain reduction score of 1.1 with highly significant ongoing long-term improvement in pain (Fig. 2, $p < 0.01$; Wilcoxon rank t test). Pre-treatment pain was increased on Mondays after the weekend break. One month after complet-



FIG. 1. Application of cold atmospheric argon plasma (MicroPlaSter β) to the ear channel.

ing CAP treatment, the patient remained highly satisfied with the result.

During the total 105 day plasma-treatment period, bacteriology swabs from the external auditory canals and nasopharynx were all negative. Specifically no ESBL-producing *E. coli* were detected. However 3 weeks after the final plasma application, *Propionibacterium acnes* was cultured from the external auditory canal and ESBL(+) *E. coli* from the nasopharynx.

Despite antibiotic prophylaxis, surgical site infections occur in head and neck cancer surgery in over 30% of cases [8]. The battle against antibiotic-resistant bacteria is one of the greatest

challenges in medicine in the 21st century and new approaches are required to manage this problem [9, 10]. CAPs may be an option as they can achieve high antibacterial activity without the development of resistance (neither showing primary nor secondary resistance development) or harmful effects on surrounding human tissue [11–13]. The effects are probably due to a synergy of physical–chemical features resulting in cell wall permeabilization, penetration of reactive oxygen and nitrogen species, and subsequent chemical reactions and actions inside the cell [13].

The broad antimicrobial benefit of CAP has been demonstrated in randomized controlled clinical trials in patients with chronic wounds [6, 14]. CAP application in Hailey-Hailey disease resulted in successful clearance of *Proteus mirabilis* and *Candida albicans*, and reduction in pain and burning sensations due to the impetiginization [15].

In this case report, plasma application was limited by the diffusion and penetration of the plasma into the external auditory canal, and the inability to treat the nasopharynx. However, even in a set-up not primarily developed for the treatment of the external auditory canal, CAP treatment resulted in the clearance of bacteria and relief of symptoms of infection during treatment. Long-term antibiotics could be ceased and quality of life improved to a patient's satisfaction.

The current report will be advanced by future studies demonstrating the efficacy of CAP sources designed for treat regions that are difficult to treat, such as the external auditory canal, and safety of use in the oral cavity.

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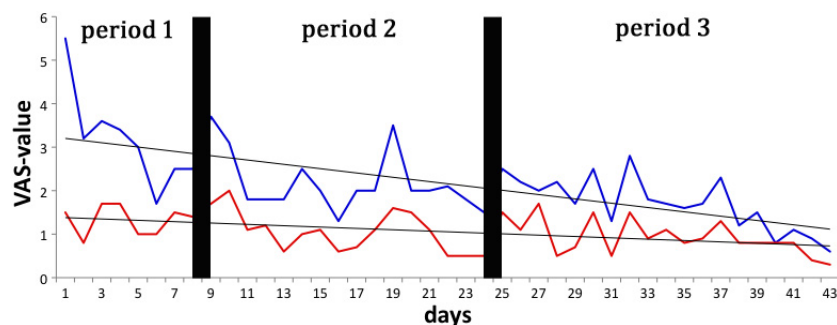


FIG. 2. Highly significant reduction of pain after plasma application (43 applications, mean reduction 1.1, $p < 1.1 \times 10^{-8}$). Blue line: pain according to VAS (range 0–10, where 0 corresponds to no pain at all and 10 to the most severe pain imaginable), before plasma application; red line: pain after plasma application; grey line: linear trend line. VAS, visual analogue scale.

bacterial specimens. We thank ADTEC Plasma Technology Co. Ltd., Hiroshima, for the allocation of the MicroPlaSter β device.

Transparency Declaration

The MicroPlaSter beta device was provided by the Max Planck Institute for Extraterrestrial Physics. The following authors are designated inventors and patent-holders of the plasma applicator and corresponding method: G.I., T.S., G.E.M. and W.S.

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