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REVIEW ARTICLE

Plasma Therapy: An Overview

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ABSTRACT

Definition: Plasma, the fourth state of matter, is a collection of charged particles (electrons, ions, neutral atoms). Recent demonstration of plasma technology in treatment of living cells, tissue and organs are creating a new field at the intersection of plasma science and technology with biology and medicine known as plasma medicine. Plasma medicine is one of the newest fields of modern applied plasma chemistry. It appeared several years ago and comprises studies concerning the direct action of low-temperature, one atmosphere air plasma (cold plasma/nonthermal plasma/nonequilibrium) on body tissues for various noninvasive therapeutic treatments or diagnostics purpose. The study of plasma holds promise for a myriad of applications ranging from lasers and electronics, hazardous decontamination, sterilization and disinfection of foods, soil, water, instruments, to medical uses in wound healing and treating certain types of tumors and cancers. Plasma represents a new state-of-the-art sterilization and disinfection treatment for certain oral and environmental pathogens, heat-sensitive materials, hard and soft surfaces, and may assist health care facilities in the management of various health concerns. The role that low temperature atmospheric pressure plasma (LTAPP) could play in the inactivation of pathogenic microorganisms might prove to be a new, faster, more economical alternative.

Keywords: Cold plasma, LTAPP (low temperature atmospheric pressure plasma), Nonequilibrium.

INTRODUCTION

Plasma, known as the fourth state of matter, is the least recognized, yet most prevalent form, occurs commonly in nature, assuming in forms of fire, lightening or stars, making over 99% of the universe. Plasmas represent a 'cosmic soup' of fixed and freely moving electrons and ions, various active species (exited atoms/molecules, radicals) and energetic UV photons. Free electron gain energy responding to electric and magnetic and heat up, reaching typically very high temperature (10,000-100,000 K). Most forms of plasma are not easy to test because they are extremely hot and difficult to manipulate, but currently, researchers are developing techniques to produce low heat plasmas that can be manipulated at room temperature and atmospheric pressure.[1,2]

HISTORY

The English physicist Sir William Crookes identified plasmas in 1879, although it was an American physicist, Dr Irving Langmuir who first applied the word 'plasma' to ionized gas in 1929. In the late 1850s, the Siemens company used plasma discharge to generate ozone, which acted as an agent to remove contaminants and toxins from water. Nevertheless, for the next 100 years, little research was conducted exploring the relationship between plasma and biological cells. From the 1960s to 1980s, plasmas were mainly utilized as a secondary agent to indicate biological sterilization, yet diminutive cause and effect knowledge was advanced. It was not until the mid-1990s that scientists made considerable progress in cold plasma technology. As the news of plasma science spread, visionary researchers took notice and began to explore various ways to utilize plasma's unique properties. Plasma science was in its infancy in the 1990s, but by 1997, multidisciplinary teams set out to understand the effects that plasmas had on pathogenic and nonpathogenic microorganisms, as well as develop proof of concept studies to demonstrate that plasma could be used as a decontaminant or sterilizing agent. Since the late 1990s, plasma research has evolved at a rapid pace as technology expanded into areas, such as biomedical, environmental, aerospace, agriculture and the military.[3,4]

PLASMA FOR BIOMEDICAL APPLICATION

The direct action of plasma on the body means that the living body tissue directly participates in the discharge generation

process, acting as the second electrode under a floating potential. The high-voltage electrode in the discharge, which is kind of a dielectric-barrier discharge (DBD), value determined by the electrical safety regulations. Such a discharge, which is completely harmless for the human body, possible applications are wound sterilization, blood coagulation, treatment of cosmetic diseases, regeneration of destructed tissues, selective programmed killing of cancer cells (apoptosis), diagnostics of skin diseases, etc.[5]

Wound Sterilization

Investigators have used scanning electron microscope (SEM) to visually inspect the impact that plasma exposure may have on cell morphology. Any visible change in outer structure of cells after exposure to plasma was attributed to the impact of a specific plasma agent. By using SEM images, Laroussi et al[6] showed that after exposure to plasma, *E. coli* cells underwent severe morphological changes, such as lysis (splitting of cells). SEM had shown lysed *E. coli* cells after plasma treatment. Laroussi et al attributed such damage to one of two processes—membrane rupture due to charge build up on the cells or to chemical attack by radicals such as O and/or OH.

Blood Coagulation

Blood coagulation is the most important factor that determines wound healing. High-temperature plasma is used for thermal blood coagulation for many years. However, the thermal treatment is always accompanied by tissue damage near the wound. Low-pressure plasma is used for the *in vitro* sterilization of medical ware. Recently, it has been shown that low-temperature DBD treatment significantly accelerates blood coagulation and leaves the adjacent tissues intact. A drop of blood drawn from a healthy donor coagulates on its own on steel substrate in 15 minutes. The treatment of the drop surface by DBD (dielectric-barrier discharge) causes the complete blood coagulation in 1 minute. It was shown that the structure and the properties of proteins involved in the coagulation cascade are substantially changed by the action of DBD.[5,7-9]

Wound Healing

Plasma leads to generation of a significant concentration of NO in an atmospheric air flow. The Plazon device designed for this purpose by Shekhter et al not only was widely tested in animals, but also passed clinical tests in different areas of medicine. The performance of Plazon can be exemplified by its use for the treatment of venous and arterial trophic ulcers. The clinical tests were carried out in 318 patients with trophic ulcers of the vascular etiology. The patients were subjected to treatment for 10 to 30 days with exogenous NO at its concentrations in atmospheric air of 0.3 to 0.5%. The cleansing of the ulcers from necrosis and exudates and appearance of granulations and boundary epithelialization were accelerated on average by 2.5 times in the NO therapy. The duration of complete healing decreased by a factor of 2.5 to 4 times depending on the ulcer size.[5,10,11]

CANCER CELLS

The treatment of melanoma cancer cells with a low power DBD, which does not cause direct cell destruction can, however, initiate apoptosis—the cascade of biochemical processes resulting in cell death not immediately but in several hours or even days after the treatment. The neighboring cells are not involved in the process, and no immune reactions, including inflammation, are initiated. The melanoma cells were cultured in a culture medium in a Petri dish. The solution was exposed to DBD treatment. Microphotographs of the cell medium containing melanoma cells in 24 hours after the DBD treatment for 5 seconds and of the control sample of the same concentration showed that 22.5% of the melanoma cells decayed in 24 hours in the treated sample *vs* the death of only 2.2% of cells in the control. In 72 hours, the amount of the dead cells was 72.8 and 3.2% respectively. This indicates that the apoptosis is caused by the direct action of the discharge on the cell during the treatment. Using the selectivity of plasma treatment, one can find treatment conditions at which only cancerous cells will decay via apoptosis, whereas healthy cells will remain undamaged.[5,12]

Laser-induced Plasma

Today, lasers are used in tissue cutting, blood coagulation, photodynamic cancer therapy, arterial plaque removal, dental drilling, etc. In this paper, we examine those areas of laser medicine in which plasmas (ionized gases) are produced. In fact, the presence of plasma is essential for the application at hand to succeed. We consider examples of the plasmas produced in urology (e.g. kidney fragmentation) (Fig. 1), cardiology and vascular surgery (e.g. laser ablation and removal of fibrofatty and calcified arterial plaque).[13]

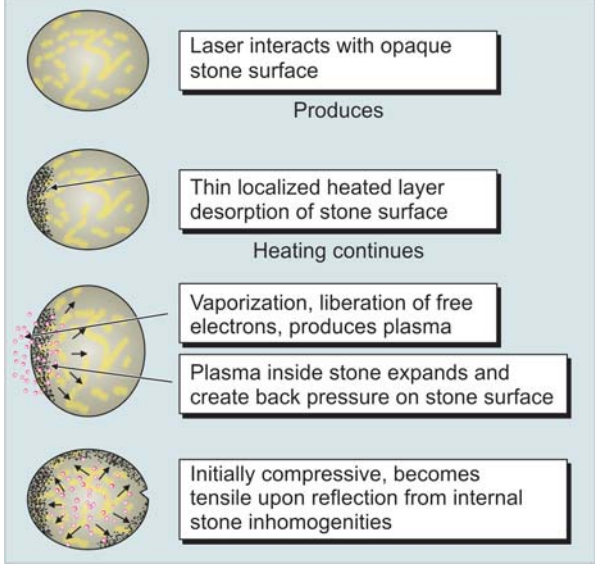

Fig.1: Proposed mechanism of action of plasma in removal of calcified plaque and kidney stone

PLASMA IN DENTISTRY

Rise in Temperature during Cavity Preparation

Nonthermal atmospheric plasmas operate at room temperature and do not cause pain and bulk destruction of the tissue. Plasmas can treat and sterilize irregular surfaces; hence, they are very suitable for decontaminating dental cavities without drilling. The advantage of this novel tissue-saving treatment is that although the plasma itself is superficial, the active plasma species it produces can easily reach the inside of the cavity. In contrast to lasers, plasmas can access small irregular cavity and fissure spaces. Temperature in the tooth during plasma treatment and the efficiency of the plasma in killing bacteria are investigated by use of portable plasma needle (Fig. 2). At 220 mV (before thousand times amplification), the temperature rise is about 2.3° C, which should be safe according to Zach and Cohen.[10] In general, these data suggest that the temperature increase in the pulp of a tooth can be kept within the safe range. The temperature was determined in a stationary situation, without blood flow through the tooth. The latter might affect the results due to convection effects. In the next step, temperature measurements in an irrigated tooth preparation will be performed. It is expected that convection will further reduce the heating of the tooth.[14] Firing low-temperature plasma beams at dentin was found to reduce the amount of bacteria by up to 10,000-fold.The findings could mean plasma technology is used to remove infected tissue in cavities.

Bacterial Decontamination

Plasma Treatment of Streptococcus Mutans Biofilm

The *S. mutans* biofilms were grown with and without 0.15% sucrose. A chlorhexidine digluconate rinse (0.2%) was used as a positive antimicrobial reference. A single plasma treatment for 1 minute on biofilms cultured with no sucrose caused a bactericidal effect. Also, with either single or repeated plasma treatments of 1 minute on biofilms cultured with 0.15% sucrose, growth was reduced. In the study, plasma effects were evaluated by monitoring growth responses of the biofilms after single and repeated treatments. the regrowth of bacteria after a single plasma treatment caused a bactericidal effect (no regrowth) against *S. mutans* biofilms. The degree of inhibition is probably related to the thickness and age of the biofilm culture. A thicker biofilm would present a greater challenge for the penetration of plasma radicals. *S. mutans* biofilms grown in presence of sucrose synthesize glucan ex-polymers which result in a thick, 'sticky' biofilm. This could impede the antibacterial activity of plasma, killing cells only at the surface and inducing a sublethal response to cells attached to the surface. Chlorhexidine, regarded as the 'gold standard' anti-plaque treatment, is an aggressive chemical, which when used topically can lead to desquamation and soreness of oral mucosa. Its future as a caries treatment is being questioned and unless heavily applied, it is ineffective in treating childhood caries. A safe and less aggressive alternative treatment to chlorhexidine would be higly desirable. Plasma was found to be by far more effective than chlorhexidine.[15]

Fig.2: Placement of plasma needle in pulp chamber

Sterilization of Dental Instrument

The risk of prion transmission via surgical instruments is of current public and professional concern. These concerns are further heightened by reports of the strong surface affinity of the prion protein, and that the removal of organic material by conventional sterilization is often inadequate. Recent reports of contamination on sterilized endodontic files are of particular relevance given the close contact that these instruments may make with peripheral nerve tissue. Prion diseases are a rare group of fatal diseases, which in humans include, familial, sporadic and acquired Creutzfeldt-Jakob disease (CJD). The disease is characterized by accumulation of an abnormal form of prion protein in the central nervous system. While abnormal prion protein (PrPSc) could not be detected in the dental pulp tissue of sporadic CJD patients, no studies have been reported with patients incubating variant CJD where typically the levels of PrPSc, and thus of infectivity, in peripheral tissues are higher. Indeed, Ingrosso et al have shown that the gingival tissue and dental pulp of hamsters infected with experimental 263 K scrapie prion by intradental injection are highly infective. Thus, there is a theoretical risk of CJD transmission in humans occasioned by reuse of dental instruments, such as endodontic files, which could come into intimate contact with peripheral nerves. As there are no published data on the possible risks of prion disease transmission via such files, the presence of any protein material on these instruments represents a theoretical source of iatrogenic CJD transmission. Use of plasma decontamination of surgical instruments has been limited. This preliminary study, which we aim to extend, has indicated that the use of gas plasma cleaning may be extremely beneficial in reducing the absolute amount of proteinaceous materials that may be transferred between patients when endodontic files are reused.[16]

DISCUSSION

As plasma has shown potential of inactivating bacteria, sterilization, wound healing, in blood coagulation, over malignant cells, why not the same can be utilized for the same purpose in dentistry? As the dental professionals too need to overcome above-mentioned complication and if plasma can remove kidney stone and fibrofatty calcified tissue from arteries in cardiovascular disorder, why not the same can be utilized for the purpose of sialoliths in salivary gland and calcified plaque in various periodontal diseases? Although it is not sufficient to include all the aspect of plasma therapy in this paper, it is sad to say that we are still far away from an implacable dental and medical plasma application, it is just an intent to create an awareness towards safe, developing, efficient and echo-friendly plasma technology.

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