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The Plasma's Promising Future in Biomedicine – Review

Amani Abduljabar Altaie [(1)] *
Amjad Luqman Alhayaly [(2)]
Emad Farhan Alkhalidi [(3)]

[(1,2,3)] Department of Conservative Dentistry, University of Mosul, Mosul, Iraq.

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***Corresponding Author:**
Email:
amani.abduljabar@uomosul.edu.iq

MSc. Student in Department of Conservative Dentistry, University of Mosul, Mosul, Iraq.

Abstract

Background: It is common to refer to plasma as type of matter its fourth shape of materials. Plasma is found in universe naturally in many forms and con be produced artificially, which has become more significant in the fields of plasma screens and light sources. It is a commonly used disinfectant in clinics due to its abundant in nature and possible antibacterial qualities.

Highlight: We focus on definition of plasma, history, types of plasma according to the temperature, methods of production and its applications in medicine such as deactivate microbe, cancer cell death, and cell separation, and in dentistry especially such as modifications of dental implants surface, increase adhesion of dental materials, disinfectant and sterilization of surgical instruments and endodontic files, root canal disinfection and sterilization , modification of polymerization of composite resin, post surface modification, teeth whiting. This study illustrates how low air pressure and low temperatures directly affect body tissues throughout a variety of non-invasive medical procedures and tests.

Conclusion: Given that Cold Atmospheric Plasma contains antimicrobial and cell-killing qualities, we can conclude that dentistry will benefit greatly from it. Research on Plasma has demonstrated encouraging outcomes in the areas of composite restoration, instrument sterilization, tooth bleaching, and deactivation of dental biofilms.

Introduction:

What is plasma exactly? There are three state of material that are commonly recognized: liquid form, solid form, and gas form. The term "fourth state" is frequently applied to plasma. Particles in the plasma state are found in plasma, a gas. It might be described as a gas that has ions, free electrons, and other radicals that are active in atoms or molecules, such as hydroxyl radicals (OH-) (1,2), Intense transient electric fields and energetic photons, or ultraviolet light, are also present in plasma. Due to the significantly lower electric field in pulsed discharge, both are necessary for the creation of reactive species or the breaking of bonds (3,4).An interdisciplinary topic of study called "plasma medicine" looks into the applications of plasma in the medical industry. Currently, atmospheric pressure applications are the primary focus of non-thermal plasma technology with direct applications have been utilized for food decontamination(5,6), and surfaces in contact with food (7), in the food sector, as an antibacterial agent in the medical and dental disciplines, and in air purification (8). Non Thermal Plasma (NTP) without any thermal harmful effect or discomfort to patients because it does not raise the temperature at the application site. Its use enables the treatment of non-homogenous, heat-sensitive surfaces. as well as living tissues. Applications in medicine include broad-spectrum anti-itch properties. technology that fights bacteria, reduces inflammation, stimulates tissue, improves blood flow, and consequences of proapoptosis, improvement of wound healing through increased cutaneous microcirculation, keratinocyte growth, and activation of monocytes(9). Plasma is capable of fighting tumor growth by boosting antitumor treatment drugs' effectiveness, reactivating Apoptotic pathways or growth-related gene locations that are downregulated (10).

History of plasma

In 1879, Sir William Crookes, a British scientist, discovered the fourth shape of substance and Irving Langmuir named "plasma" to this shape of matter in 1924. Particles that have been removed are called plasma. When the molecules and atoms lose its electrons transform into plasma and this process need energy to remove electrons, so disappear of energy lead to rejoin of electrons to molecules and atoms and produce gas state again (11). In 1929, Dr. Irving Langmuir, an American scientist, coined the term "plasma" to describe ionized gas. The Siemens Company used plasma discharge in the late 1850s to produce Ozone, and it served as a contaminant-removing agent. harmful pollutants found in water. However, for the following 100 years, not much research was done to examine the plasma and biological cells' connection. The primary use of plasmas during the 1960s and 1980s was as a secondary agent to suggest biological sterilization, but knowledge of the cause and effect was somewhat improved (12). When word of plasma physics spread, creative scientists noticed and started investigating different applications for plasma's special qualities. In the 1990s, plasma science was just getting started, nevertheless, by 1997, many researches wanted to explain how plasmas affected both pathogenic and non-pathogenic bacteria(13). In the late 1990s, as technology has advanced into new fields, like as such as the military, aerospace, biomedical, environmental, and agricultural (14).

Feature and Function Overview for Plasma

The physical efficiency of plasma is enhanced by the creation of ions, electrons , and UV radiation; also, free radicals have a potent oxidative effect on the cell's outer components (15). Indeed, the integrity of the bacterial cell's membranes, coatings, and walls can be seriously compromised by charged particles produced by plasma (16), which can lead to the inactivation of microbes (17). The direct application of plasma therapy to tissues or cells has the ability to modify cellular activity in both prokaryotes and eukaryotes. This allows for the control and manipulation of biological processes that are essential for the creation of biofilms, tissue regeneration, and carcinogenesis (18) . Additionally, osteoblast-like cells which were grown on titanium substrates treated with CAP and able to generate substantially improved cellular structures showed increased cell spreading, proliferation, and generation of extracellular matrix proteins as a result of plasma therapy (19).

Classification of plasma

Plasma can be classified according to the temperature of production in to:

1)High- temperature plasma: every particle in a high-temperature plasma, which has the same temperature including electron and heavy particles they are together in thermal balance state (20).

2)Thermal plasma: Only certain areas of thermal equilibrium exist in thermal plasma; The temperature range of (10,000 K-100,000 K) is common, limiting the gas's utility, as all of its energy is utilized to heat it. Furthermore, the gas has the same temperature for both heavy particles and electrons such as ions and neutrals (21). This is an occurrence of high-intensity electrons and ions that are thermally balanced. For a long time, the establishment of hemostasis in medical research has been dependent on hot plasma techniques such as electro surgery and coagulation (22).

3)Non-thermal plasma(low-temperature): Particles in non-thermal plasma are not in thermal balance state. This plasma is referred to as "cold atmospheric plasma" (CAP); at normal temperature, it only contains heavy particles producing a < 40 ◦C point of application (23). Nitrogen, oxygen, hydrogen, and argon are the most frequently utilized sources of plasma gas. In material science, low-temperature plasmas can be used to add or modify chemical groups that are attached to surfaces, as well as to change surface properties such as electrochemical energy or degree of oxidation. Therefore, it is possible to safely and accurately alter affinity towards specific chemicals by utilizing features of materials like resistance to physical or chemical, hardness, abrasion or corrosion, water absorption capacity, low temperature and wettability(24).

Application of plasma:

In the recent years, there were numerous efforts to introduce plasma in biological sector. Numerous relevant studies on the handling of biological materials, genetic transfection, cell adhesion, and cell surface differentiation (25):

1 Systemic Application: plasma can be applied in many medical fields like Oncology, plasma induced tumor cells death (necrosis, apoptosis, senescence, and autophagy) as well as lessen cancer cells' ability to adhere, migrate, and invade in a dose-dependent way, which lowers cancer cell diffusion and metastasis-forming capacity . Also plasma can use for treatment carcinomas of squamous cell for the neck and head with an emphasis on pain management and lesion regression (26). Dermatology is a distinct branch of medicine since it doesn't harm the skin's protective layer, decreases skin moisture, and uses plasma to accelerate tissue granulation and improve wound healing.

While encouraging, many studies are needed to make the dermatological application of CAP more stable and effective over time (27,28).

2 Dental (Oral) Application: When Goree et al. originally introduced the idea of employing CAP for novel dental operations, it caught the attention of dental researchers (especially in endodontic field) (29):

-Root Canal Disinfection: Good treatment outcomes in endodontic case depend on the canal's walls and lumen being good irrigation and cleaned. Recently, cold atmospheric plasma has been tried as a novel disinfecting mode for the system of root canal, Lu et al. created plasma inside root canal by using device of plasma jet, It would be painless to use bare hands to touch and physically guide the plasma into the root canal to clean the area, It has been documented that bacteria can reach dentinal tubule depths between (500 µm–1000 µm) (26). NTP containing helium/oxygen (20%) gas was used, the findings revealed temperature rotation about 300K with temperature vibration of about 2700K. Under these circumstances, a discharge of (10 mA) peak current is frequently observed. According to initial deactivation research outcome, this degree of plasma production is lethal to Enterococcus faecalis, which is the primary germs causing root canal treatment failure, totally in a matter of minutes (30).

-Sterilization of Instruments: the effect of plasma in sterilization depended on frequency, bacterial stain, and gas composition of plasma, it has been discovered that plasma devices kill bacteria more quickly than traditional methods (steam autoclave, dry heat and chemical vapors). The process of sterilization by plasma depends on its constituents, such as electromagnetic fields, electrons, ions, ultra-violet, and reactive oxygen species (ROS) (31). Proteins and unsaturated fats participate in membrane transport in the lipid bilayer found in the membrane of bacteria, attacks by hydroxyl radicals on fatty acids which are not saturated, that are generated by plasma and damage the lipid in cell membrane, render bacteria dormant. Plasma may also have an impact on the area surrounding the point of contact (32).

- Dental Caries: Free radicals released by plasma help remove pathogens from the caries body while causing the least amount of tissue harm, Govil and colleagues examined the reaction between plasma generate from plasma needle and dental tissue. Irradiation with plasma readily penetrates the constructed cavity to its full depth, so bacteria that cause dental cavities are reduced when low plasma temperature beams are fired into dentin (33).

- Tooth Bleaching: A plasma jet at atmospheric pressure was produced by Lee et al. and used to improve the bleaching impact of hydrogen peroxide on teeth (34), Hilum also uses as working gas at rate of flow about 2slm. The plasma treatment eliminated the protein from the surface of tooth, as shown by Scan electron microscope and staining of Ponceau S, also they illustrated that the plasma jet enhanced the degradation of hydrogen peroxide (H_2O_2) in many experiments (35).

- Removal of Biofilm: Bacterial biofilms consist of consortia of adherent microorganisms encased in polymer matrixes that the bacteria manufacture themselves, which are composed of proteins, lipids, polysaccharides, and extracellular DNA, and it's the main factor for dental caries, gingivitis and periodontitis. Without endangering the oral tissue, NTP can degrade the biofilm matrix (36). Dental implant biofilms can be effectively removed by combination of plasma treatment with no abrasiveness air or spray of water, as found by Rupf et al. (37). In a different investigation, Koban et al. study shown that exposing of S. mutans (which is constituting of dental biofilms) to cold atmospheric Plasma had more effect than that with chlorhexidine. NTP is also effective in removing biofilms from dental slices and root canals (38).

- Polymerization of Composite Restoration: preliminary evidence indicates that plasma treatment around 60% elevates bonding strength at the dentin/composite interface (39). Enhancing interface-bonding to greatly increase the performance, lifespan, and durability of composites, Dentin surface modification with atmospheric cold plasma brush (ACPB) therapy can improve dentin/adhesive interfacial adhesion. The resolution is to add linkages that are not dependent on surface porosity but rather on surface chemistry (40). Adhesive bonding is improved by plasma irradiation by producing micro-structural and chemical changes that create a thin plasma coating on the dentin and enamel surfaces that promotes bonding with composites (41).

- Adhesive of Post and Core: According to the study of Yavrich et al., NTP treatment of core enhance shear bond strength with composite because NTP increase wettability of core and roughen its surface and this effect depending on time of exposure to plasma but NTP cause post- surface aging and its technique sensitive (2).

- Treatment of Periodontal Disease: Direct application of NTP has been demonstrated by Koban et al. to decrease liquid contact angle of the non-treated dentin surface, resulting in increased proliferation of osteoblast on dentin. These investigations may be applied for regeneration the vital tissue of periodontal portion. The relationship between mesenchymal stem cells of human periodontal ligament and NTP was demonstrated in study of Miletic et al. The researchers did find that NTP did not affect cell viability but inhibited the cells' ability to proliferate while simultaneously encouraging their osteogenic differentiation (42).

- Repair of Denture Base: Heat-cured acrylic resin is not adequately bonded to chemical cure acrylic resin, that is used to treat a cracked denture foundation, so in order to strengthen the binding of heat cured acrylic resin to chemical cure acrylic resin this found in study of Nishigawa et al. when applied a plasma to heat cured acrylic resin for about (15 seconds). Furthermore,a study was conducted to investigate the adhesion between the cobalt-chromium alloy and self-curing acrylic resin. Nevertheless, the plasma treatment had negative effect on the materials' adherence to one another (43).

- Treatment of Intra-Oral Disorder: Candida-related stomatitis of denture, angular stomatitis, linear gingival erythema and median rhomboid glossitis, are among the conditions linked with oral candidiasis. Yamazaki et al. and Koban et al. revealed that employing a variety of plasmas to sterilize Candida albicans was highly effective. Their findings suggest that plasma jets may be able to treat Candida albicans-related stomatitis (44)(45).
Consequently, Non-Thermal Plasma with its potential in treatment of intra-oral disorders, many researches are needed to accurately determine how it affects a wide range of oral and dental ailments.

- Oncology: due to its capacity to produce ROS (Reactive Oxygen Species) and RNS (Reactive Nitrogen Species) and hence cause the selective death of malignant tumor cells, CAP is used in oral cancer (46). A group of the effects of the cold atmospheric Plasma in tumor cells (47):
A. Stimulation of Protein 53.
B. Initiation of inhibitor Protein 21CDK.
C. Cause the cell life cycle stopping at the G2/M and S phases.
D. Elaborate of ROS (Reactive Oxygen Species), DNA damage, and inhibition of cell replication.
E. Activation of apoptosis because the production of ROS mitochondrial and turning the mitochondria.
F. Lowering in potential of mitochondrial membrane, decrease cellular respiration in tumor cells and activity of mitochondrial enzymes.
G. Disturbance in the concentration of ROS (Reactive Oxygen Species),and fluid lipid peroxide found intra-cellular.

- Surface Treatment of Implant Fixture: Dental implant made by titanium can be sprayed by plasma to create rough surface for better adhesion of bone cells (osteoblast, osteocyte) to increase osteointegration, bone formation around implant and decrease time required for this process. Plasma spray coating is one coating technique that involves spraying molten materials (such as Calcium phosphate) onto surface of implant (28). In order to enhance-integration, the technology of plasma is using to modify the surface of implant fixture. Efforts are being undertaken to accelerate the early host-to-implant interaction since the surface of implant fixture is the first part to engage with the host tissue. The justification for its alteration centers on interaction of the implant with biofluids, which modifies in a positive way the series of actions that result in bone healing and close contact with the surface (48). Enhancing cell adhesion with plasma treatment can be achieved by modifying surface wettability and roughness. Titanium abutment also treated by plasma to increase reactivity and wettability of surface and decrease contact angle to enhance bonding of titanium with luting agent (49).

- Surface Treatment of Implant Abutment: The ability of Cold Atmospheric Plasma (CAP) to modify titanium surfaces' physico-chemical characteristics without compromising their microstructure, its effectiveness to decrease the liquid contact angle of plasma treated titanium (Ti) surfaces and so lead to an improvement of hydrophilic

features surface of materials surface (50) (51).
El-Helbawy et al. (52) found in his study formation of (TiO_2) layer after Oxygen plasma treatment for titanium abutment, this (TiO_2) layer increases roughness of titanium surface but with more time of plasma exposure this oxidation process becomes stable without further effect. Foest, et al. who observed that exposure to plasma will modify the chemistry and energy of material surface because more amount of reactive Oxygen species (O_2) that generate on treated surface that caused chemical bond with the resin cement (53).

- Zirconia crown Surface Treatment: The plasma surface treatment lowers moisture content in plasma gas and environment with electrons of high energy to produce (OH) radical, which decreased the amount of hydrocarbons adsorbed. The removal of organic impurities on the surface of zirconia leads to destruction of Carbone-Hydrogen bond (C–H) and Carbone-Carbone bond (C–C) bonds may have an important role in improving the bonding of plasma treated surfaces (54). This agrees with Kim et al.'s XPS (X-ray photoelectron spectroscopy) investigation which observed that low percentage of carbon of plasma treated zirconia was less than that of non-treated zirconia surface and high oxygen percentage because plasma eliminate organic impurities that contain carbon, so O/C ratio was higher in plasma treated zirconia and it had good wettability because O/C ratio is good indicator for wettability of surface(55). Study of Majeed and Jassim (56) that found the wettability test findings indicated that the liquid contact angle of the zirconia surface decreased, that mean enhance the surface's wettability also rise in surface energy of zirconia. There are many justifications for this phenomena as increase in concentration of active particles (O_2), groups such as (C-O) and (C-OH) and peroxide radicals on the Zirconia surface treated with plasma, that lead to elevate Surface Energy (SE) in the surface lead to increase the polarity, that supported by EDX (Energy dispersive -ray) results of Mahrous, et al.(57) study and XPS analysis (X-ray photoelectron spectroscopy) by Noro, et al. study (58).

- Plasma-Treated Water: The phrase "treated" describes the removal or total mineralization of harmful germs, pharmaceutical compounds, and synthetic colors from wastewater, among other pollutants. Consequently, Large or small volumes of water can be cleaned or decontaminated via plasma water treatment (59), Application of water activated with plasma in dentistry are: anti-Inflammatory properties and wound healing, treatment of infectious diseases which found in the mouth, decontamination of dental instrument, used in tooth bleaching and anti-cancer therapy (60).

Conclusion

In the biological field, the ability of cold plasma to interact with subjects in a non-destructive manner on a physical, chemical, and biological level is highly valuable. The use of plasma in dentistry has been investigated for adhesion, caries therapy, endodontic treatment, tooth whitening, and surface alterations of dental implants. Still, pertinent dentistry research is early started. Research needs to be done on the basic ideas underlying how plasma affects tissues, cells, and the live organism as a whole, further research is needed to determine the optimal breadth and depth of the plasma plume in order to facilitate posterior tooth penetration.

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