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Review of the Current State of Medical Plasma Technology and its Potential Applications

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Plasma technology is entering a new chapter through medical use. Medical devices based on plasma technology have recently been tested for the biochemical effects of plasma on cells and tissues. The implementation of plasma technology in medicine was made possible by the introduction of non-thermal, cold plasma emitted at atmospheric pressure. To date, the putative biological effects of plasma include decontamination, disinfection, tooth bleaching and accelerated wound healing. In addition, cold plasma treatment has some potential as a novel cancer therapeutic. Plasma is currently believed to exert its diverse effects mainly by regulating both intra- and extracellular oxidation-reduction reactions as a result of the generation of reactive oxygen and nitrogen species. Interestingly, the biological effects of plasma exhibited hormesis, which is a biphasic response depending on the degree or amount of exposure. Ongoing investigations focus largely on elucidating how the modulation of oxidation-reduction by plasma affects the behavior of cells and helps determine the optimal treatment parameters maximizing the favorable effects of cold plasma. Although accumulating evidence indicates the role of cold plasma as the next-generation therapeutic in various medical fields, more detailed characterization of the biomolecular effects of plasma appears to be the next critical step, along with clinical studies designed to validate its clinical efficacy and safety.

Key words

Plasma medicine; Non-thermal plasma; Reactive oxygen and nitrogen species; Wound healing; Oxidation-reduction

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INTRODUCTION

Medical therapeutic devices have long benefited from advances in technology and engineering. A vast number of devices that are readily used were first made as products of cutting-edge technology of that time. For instance, laser devices, which stand as the cornerstone of aesthetic procedural dermatology, could not have been introduced if it were not for the technicians and engineers who made the principle of selective photothermolysis from theory to reality. More recently, radiofrequency devices have and brought about waves of new machines that combine radiofrequency with other modalities.

Though one may think there already are enough treatment modalities for every medical need, fulfilment of a certain need often unmask a new one. Also, there is no medical device that ensures the best clinical outcome for every patient. Hence, the more treatment modalities the clinician has in hands, the better will the clinical results be.

Plasma technology has recently made considerable progress in medicine. The first implementation of the plasma technology dates back to the 1970's, when it was originally used as a surgical cutting device. Since then, medical doctors, scientists and engineers have strived to identify the biological effect of plasma on cells, seeking for its medical uses. As a result, plasma technology is being tested for its use for various indications ranging from decontamination to cancer treatment. So far, there have been reports of some promising results. However, it is certain that there is a long way ahead before plasma can fully be incorporated into medicine

Here we review the literature on the current state of plasma medicine, with a particular focus on its possible clinical indications.

METHODS

A systematic literature review was performed based on Pubmed/Medline and Embase. A thorough search of the database was made by using 'plasma jet', 'cold plasma', 'low-temperature plasma', 'atmospheric pressure plasma' as key terms. Articles published either in English or Korean were included. Included articles dated between 1973 and 2017. Citations of these articles were reviewed manually in search for additional articles.

MEDICAL APPLICATION OF PLASMA TECHNOLOGY

Plasma scalpel

The very first medical device that used plasma technol-

ogy was the plasma scalpel. Introduced in the early 1970s, this instrument generates a very hot gas jet, reaching above 3,000°C.¹⁻³ Surgeons have evaluated the usefulness of plasma scalpels on animals as well as on humans and demonstrated that plasma scalpel effectively cuts tissues, and cauterizes blood vessels at the same time. As a unique clinical tool, plasma scalpels are still actively used in operation rooms.

Skin decontamination

Plasma jet was previously used medically for disinfection and sterilization of medical instruments.⁴⁻⁶ As the low-temperature plasma, sometimes also referred as 'cold plasma' emitted at atmospheric pressure was developed, electrical plasma discharges were applied on living cells, then on tissues. Similar to its original effects, low-temperature plasma showed antiseptic effects that range from bacteria to yeast and fungus.⁷⁻¹² While 'hot plasma' demonstrated its antiseptic action by its extremely high temperature, 'cold plasma' is thought to act by the abundant production of free radicals, which are toxic to organisms. Interestingly, in a recent *in vitro* experiment testing the antimicrobial effect of plasma of both methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), low-temperature plasma reduced the growth of both strains, while MRSA was found to be less susceptible. This finding potentially raises questions on the mechanism that lies under plasma's bacteriocidal property, which still remains to be investigated further.

Tooth bleaching

Although this review is intended to be read primarily by medical doctors, tooth bleaching by plasma needs to be mentioned, if not emphasized, as it sheds light on the chemical effect of plasma exposure. Numerous methods are currently available for the restoration of natural tooth color. Low-temperature plasma has been tested for its tooth bleaching effect and has produced successful results.¹³⁻¹⁵ Hydrogen peroxide, being one of the oldest bleaching technique, has long been used for tooth whitening and works by producing free radicals. Plasma treatment produces abundant free radicals and is accordingly thought to bleach teeth in the same manner as hydrogen peroxide. Thus, tooth bleaching is one of the many effects of free radical production by exposure to plasma.

Skin wound healing

Promotion of skin wound healing by low-temperature plasma is under active investigation. So far, promising re-

sults have been reported to literature. Originally, healing of chronic wounds were observed to be boosted by exposure to low-temperature plasma and this was thought to be made possible merely by its antiseptic effect. However, accumulating evidence suggest the direct effect of plasma on cells constituting the skin, especially fibroblasts. Fibroblasts play a pivotal role in skin wound healing by proliferation and subsequent migration to enable tissue growth. *In vitro* studies have demonstrated that plasma treatment significantly promotes fibroblast migration and, though to a lesser degree, fibroblast proliferation.¹⁶⁻¹⁸ According to a study by Schmidt et al.,¹⁸ plasma treatment attenuated gap junctional protein expression of human fibroblasts and altered their cytoskeletal configurations. The authors argue that decreased expression of gap junctional protein led to increased fibroblast motility. As for fibroblast proliferation, the reported effect of plasma treatment is inconsistent and requires further investigations. Currently, production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is considered to result in the aforementioned effects. Studies performed on murine skin wound model clearly demonstrated promotion of wound healing by plasma treatment.¹⁸ The outcome of more animals studies support the use of low-temperature plasma for the treatment of chronic wounds, such as venous leg ulcers and pressure ulcers.^{19,20} The demand for a medical device designed to promote skin wound healing is very high, and it now seems appropriate for clinical studies to be carried out in order to validate the safety and efficacy of plasma treatment on skin wounds in human.

Candidate for cancer therapy

Preliminary studies on the biological effect of low-temperature plasma on diverse cancer cells show a moderate degree of success up to date. Solid tumors, including malignant melanoma and glioblastoma, as well as lymphoproliferative diseases are being investigated for the possible therapeutic effect of low-temperature plasma.²¹⁻²³ The anti-cancer effect of plasma through apoptosis is also believed to result from the generation of ROS/RNS, which causes modulation of redox reactions. Because the understanding of intra- and extracellular redox reactions and their clinical implications is incomplete, it is still unclear how plasma acts on cancer cells. There certainly are a good number of obstacles to overcome for plasma to be used in cancer treatment. Elucidation of its biomolecular mechanism and validation of both its safety and efficacy may take time, but surely is imperative as introduction of a new therapeutic modality for the treatment

of cancer has always been an earthshaking event.

MECHANISM OF ACTION

How plasma affects living cells and tissues is not fully understood. This uncertainty could be attributed to the incomplete knowledge of how redox reactions influence cell cycle and cell behavior. Authors of previous articles on medical plasma technology assert that generation of ROS/RNS by plasma treatment changes the extracellular redox biology of the treated cells.²¹ This causes alteration in intracellular oxidation state, which triggers antioxidant-related enzymes, such as catalase, peroxidases and superoxide dismutase. The activation of these enzymes entails subsequent intracellular reactions, which are yet unknown, to eventually result in the observed effects. Reactive species have consistently been considered harmful to healthy, being tumorigenic and mutagenic.^{24,25} However, when produced up to a certain quantity, some of the reactive components were found to be beneficial.²⁶ This biphasic response where the opposite effects are produced by the same substance or condition depending on the amounts is termed hormesis and has been demonstrated in medical plasma treatment.^{27,28} Alcohol consumption is a good example of a hormetic process; at small amounts, alcohol can prevent heart disease, whereas it could potentially cause heart disease when consumed at large amounts. Hormesis thus requires thorough investigation on the critical amount or concentration that decides how the outcome will be. As a matter of fact, ongoing medical plasma research focus on determining the treatment parameters, including energy and exposure time, that yields the best efficacy with minimum risk.

SAFETY ISSUES

In 2009, Lademann et al.²⁷ reported the results of risk assessment of plasma treatment carried out both *in vitro* and *in vivo*, and suggested that plasma treatment is a safe therapeutic modality. Since then, several additional studies on the safety of plasma treatment have been done, mostly reporting an outstanding safety profile of plasma treatment without genotoxic effect *in vitro*.^{28,29} These findings collectively lessened worrisome speculations on the safety of plasma and boosted research on its biological effects when applied on living tissues.

CONCLUSION

Medical plasma technology has ever been evolving since its first introduction. The effects of plasma treatment are under active investigation across the globe. Plasma is being tried on a numerous types of cells, tissues and disease in order to identify its clinical indications. At present, elucidation of the exact effects of plasma on living cells at molecular level is warranted. The optimal treatment parameters for each medical use ought to be determined, as plasma treatment tends to show a biphasic effect. Moreover, clinical studies carefully designed to validate the safety and efficacy of medical plasma seem mandatory so that plasma can truly be incorporated as a therapeutic option. Although plasma technology is on the verge of a new era, the importance of the confirmation of its biological safety cannot be overstated.

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