Aviskaar – A Xaverian Journal of Research
Volume 13, February 2021

COLD ATMOSPHERIC PLASMA: A NOVEL WAY TO TREAT MEDICAL CONDITIONS

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ABSTRACT

Cold atmospheric plasma (CAP) is a near room temperature ionized gas. It is an innovative upcoming method used in the medical sector. CAP consists of a highly reactive mixture of ions, electrons, reactive molecules, excited species, electric fields and UV radiation. CAP is used to disinfect inanimate surfaces and prevents biofilm associated Candida infections and helps prevent community acquired nosocomial infections in health care settings. Pathogens such as Salmonella can form chemical resistant biofilms. CAP can effectively tackle this issue by 99.3%. It is a contact free, water less method that shows promise as a possible tool for rapid disinfection of materials associated with food processing. CAP finds use in dentistry. It can effectively treat, dental caries, intra oral diseases and can disinfect root canals, dental surfaces. It is useful in adhesive restorations and in tooth whitening. To date, CAP treatment has demonstrated significant anti-cancer capacity over 20 cancer types in vitro. Notable among these cancer cell lines are brain, skin, breast, colorectal, lung, head and neck cancers. In vivo studies have shown successful CAP mediated treatment for subcutaneous Xenograft tumours and Melanoma in mice. CAP can be generated by both direct and in direct discharges. Two types of CAP devices in use are based on this principle. Plasma jet and DBD (Di electric barrier discharge) and SMD (Surface micro discharge) are most popular. CAP has its own advantages and limitations. Safety of the equipment needs to be taken care of. The cost of equipment, maintenance and marketing are some of the issues at present.

Keywords. *CAP, DBD, SMD, Plasmajet, Melanoma*

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1. INTRODUCTION

There are four fundamental states of matter i.e solid, liquid, gas and plasma. Plasma is a neutral ionized gas that is composed of positively charged ions, electrons and neutral particles. As matter transforms from solid to liquid and from liquid to gas a rise in temperature takes place [1]. In certain cases, the atmospheric plasma discharge is very rapid. This leads to the creation of another category of plasma where electrons and heavy particles remain in thermal non equilibrium. This is COLD PLASMA (CAP). The heavy particle temperature of CAP ranges from 25 degrees to 45 degrees. CAP finds use in Biomedicine.

ISSN (Print): 2277-8411
ISSN (Online): 2278-1048

Several species such as Oxygen based radicals and Nitrogen based radicals are generated in CAP [2, 5].

1.1 CAP Devices

CAP is normally generated by direct or by in direct discharge mechanism.

Based on these principles, CAP devices are:

- Di electric barrier discharge (DBD)
- Plasma jet, Plasma pen, Plasma gun, Plasma pencil or needle.
- Surface micro discharge (SMD)
- Cold plasma stimulated solutions (PSA) or Cold plasma activated medium (PAM)[3,4]

1.2 Gases Employed to Generate CAP

- HELIUM
- ARGON
- NITROGEN
- HELIOX (mixture of Helium and Oxygen)
- AIR

CAP has emerged as an innovative upcoming method for use in the medical sector. CAP consists of a highly reactive mixture of ions, electrons, reactive molecules, excited species electric fields and Ultraviolet radiation [5]. It is widely used for the disinfection of fomites and keeps in check bio film associated pathogen infections. It also helps prevent community acquired and nosocomial infections in health care settings.

1.3 Use of CAP to Aid Quick De Contamination of Food Contact Surfaces Infested with Salmonella Biofilms

Cross contamination of food items stemming from persistent pathogen reservoirs is a huge risk factor in the processing environment. CAP is endowed with the unique ability to in activate Salmonella biofilms. It has been reported that a 15 S treatment with CAP could effectively reduce Salmonella bio films by 2.13 log CFu/ ml (i. e by about 99.3 %). It is contact free, water less method that does not require a sanitizer. CAP has the potential to act as a possible tool for rapid disinfection of materials associated with food processing [5, 6].

ISSN (Print): 2277-8411
ISSN (Online): 2278-1048

2 USE OF CAP IN DENTISTRY

CAP makes possible, a novel, painless method to prepare cavities for restoration with enhanced longevity [7,8]. It is capable of bacterial inactivation and non-inflammatory tissue modification. CAP treats dental caries and helps in composite restoration of tooth. It also finds use in teeth whitening. Plasma needles inserted in dental cavities can kill e. coli and Streptococcus mutans. Further, CAP is efficacious in treating intra-oral diseases, aids root canal dis infection, cleanses dental surfaces and helps in adhesive restorations [9,10].

2.1 Inactivation of Candida Albicans Infested Bio Films by CAP

Candida albicans, a fungus often grows as a bio film on almost all surfaces such as medical devices and human epithelial cells. Skin as well as superficial mucosal infections are largely attributed to this fungal group [11, 12]. It is known that Candida shows strong resistance to conventional broad spectrum anti-fungal drugs such as Amphotericin B and Fluconazole [13, 14]. CAP has emerged as a viable anti-microbial strategy to kill microbes growing on bio films. It has been reported that SMD plasma could effectively in activate Candida bio films growing on inert surfaces by 99.9% [15]. CAP could prevent both community acquired and nosocomial infections in health care settings [10, 11].

2.2 Other Uses of CAP

CAP finds use in other medical applications such as wound healing, blood coagulation, anti-bacterial treatment, endothelial cell proliferation etc. CAP plays a pivotal role in Cancer treatment [16].

3. ROLE OF CAP IN CANCER THERAPY

In vitro and in vivo studies on the action of CAP on cancer cells have been performed [16,17]. Studies indicate that the mechanism of action of cold plasma on cancer cells appear to be related to the generation of reactive oxygen species (ROS) with possible induction of the apoptosis pathway. Further it has been observed that cancer cells are more sensitive to the effects of CAP because a greater percentage of cells are in the S phase of the cell cycle [18].

4. CLINICAL APPLICATION OF CAP IN ONCOLOGY

Studies carried out in laboratories have shown that cancer cells are more sensitive to CAP treatment than normal cells. This has been attributed to ROS, expression of aquaporins and the overall cholesterol composition of the membrane [19]. Basic cellular responses such as apoptosis, growth inhibition, selective cancer cell death, cell cycle arrest, DNA and mitochondrial damage and immunogenic cell death have been demonstrated following CAP treatment [20, 21]. It is a well-known fact that plasma is capable of inducing apoptosis in cancer cells resistant to conventional chemotherapy and can therefore be used in combination

ISSN (Print): 2277-8411
ISSN (Online): 2278-1048

with other treatments to obtain synergistic and complimentary action [22]. CAP treatment has demonstrated significant anti-cancer capacity over 20 cancer types in vitro [20]. Notable among these cancer cell lines are brain cancer, skin cancer, breast, Colorectal, lung, head and neck cancers [24]. In vivo studies have demonstrated successful CAP mediated treatment for sub cutaneous Xenograft tumours and Melanoma in mice [25].

5. ADVANTAGES OF CAP IN CANCER THERAPY

One main advantage is the potential selectivity towards cancer cells. This is a vital parameter in the current era of targeted therapy. It is known that the treatment of tumours, particularly solid tumours by anti-cancer drugs faces three impediments.

- Treatment specificity
- Cancer cell resistance
- Treatment penetration

Owing to the unique physical and chemical properties of CAP, it could possibly serve as a multi modal therapeutic tool that could offer an answer to these issues [26]. CAP possibly operates through mechanisms involving P53, NF- KB, JNK or caspase pathways [27]. The use of Plasma induced chemical species and electric fields make possible an interesting tool for optimizing drug delivery. Brain and CNS cancers showed resistance to chemotherapy, radiotherapy and surgery. CAP proved highly successful in these areas [27]. In vitro studies showed significant reduction in tumour size and an Overall increase in the rates of survival. In vivo interactions were mostly performed on sub cutaneous tumour xenografts in mice [28, 29].

6. CAP INDUCES IMMUNOGENIC CELL DEATH

Tumours frequently evade surveillance of the immune system through immunosuppessive strategies [30]. CAP could elicit immunogenic cell death. It stimulates the recruitment of macrophages and cytotoxic T cells [30]. CAP is known to promote adaptive immunity in vitro against Melanoma cells. No resistance to CAP has been reported till date.

7. CAP RESTORED SENSITIVITY OF CHEMO RESISTANT CANCER CELLS TO SPECIFIC DRUGS

- CAP restored TEMOZOLAMIDE (TMZ) resistant glioblastoma cells to TMZ therapy.
- It made possible, the tumour necrosis factor related apoptosis inducing ligand (TRAIL) resistant colorectal cells sensitive to TRAIL treatment [27, 28, 32].

ISSN (Print): 2277-8411
ISSN (Online): 2278-1048

8. ACTION OF CAP AND NANO PARTICLE TECHNOLOGY TO TREAT CANCER

- CAP has made possible stronger anti-cancer activity through synergistic application with nano-particle technology [29].
- Enhanced anti-melanoma effect was achieved using CAP to treat melanoma cancer cells pre-treated with anti –Fak antibody conjugated gold nanoparticles [31,33].
- Combined treatment with PEG- coated gold nanoparticles and CAP increased cancer cell death in solid tumours [32].
- In CAP treated cancer cells, migration rate was decreased, and detachment rate increased [32].

9. SUMMARY OF CAP TREATMENT IN ONCOLOGY

CAP has shown promise as a selective anti-cancer tool. However, there is a need for the development of standardized reliable protocols for all future clinical trials. Studies are underway to develop more efficient type of plasma for each type of cancer. One of the future directions in the field of anti-cancer potential of CAP is in its action on dysplastic cells, mainly extensive lesions in critical areas where surgery would be either impossible or else way too expensive.

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