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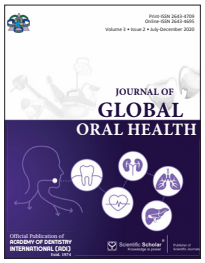

Letter to Editor

Sonoporation – The remedial sound in oral cancer

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Usage of ultrasound as an imaging technique is still in current use. However, in 1927, it came up as a therapeutic challenge when it was documented that ultrasound (ULTS) could produce eternal variations in biological systems. In therapeutic field, absorption of ultrasonic energy leads to heating of the tissue which can be used in many conditions.

Sonoporation permits the transport of therapeutic compounds noninvasively into the specific target cells by utilizing ULTS and its contrast agents (UCAs) which, thereby, improve the cell permeability.

Its principle is based on ultrasonic waves where these waves are formed in the sonoporator that converts the electric energy into mechanical or vibrational energy. The ultrasound radiation is transferred from ultrasound machine to the microparticles suspension and after transferring it efficiently produces cavitation bubbles.[1] Henceforth, these microbubbles increase transport of these huge molecules through creation of transient pores in the cell membrane enabling transport of drugs into the cell.[2]

Its advantages are it does enhanced drug penetration (of selected drugs) over passive transport, allows strict control of transdermal penetration rates, and permits rapid termination of drug delivery, skin remains intact, therefore low risk of introducing infection, less painful than injection and in many cases, greater patient satisfaction, not immunologically sensitizing, and less risk of systemic absorption than injection.

It has certain limitations in that it is time consuming, causes minor tingling and burning sensation and irritation of tissues at the site of application.[3]

Sonoporation plays various role in dentistry osteoinduction, induction of dental pulp stem cell differentiation into odontoblasts, site-specific gene delivery DNA transfer, local drug delivery, targeted drug delivery, tumor cell killing, induction of apoptosis, gene transduction, recurrent aphthous stomatitis, myofascial pain, TMJ dysfunction, lithotripsy of salivary calculi, bone healing, and osseointegration.[4]

Mechanism of action of sonoporation

Sonoporation has been reported to result in a 20–80% improvement in tumor response to drug treatment compared with administration of drugs alone in preclinical murine models. In sonoporation, hydrophobic gas-filled microbubbles, stabilized by a lipid, protein, or polymer shell, are exposed to ultrasound. During exposure, the microbubbles can undergo volumetric change and/or violent collapse, a process called cavitation. Cavitation can occur

in two forms: Stable and inertial. Stable cavitation occurs when the microbubbles oscillate stably around a resonant diameter at low acoustic intensities. At higher intensities, the microbubbles undergo much more violent expansion, contraction, and forcible collapse, generating shock waves in the vicinity of the microbubbles, a process called inertial cavitation. Both forms of cavitation can create pores on the nearby cellular membranes and vessel walls, allowing for transport of particles. In addition, the fluid motion induced during the cavitation process may enhance the transportation of drugs into the interstitium, increasing the quantities of agents that can reach more distant tumor cells.[5]

Role of sonoporation in cervical cancers

Therapeutic efficacy of both traditional chemotherapy and gene therapy in cancer is highly dependent on the ability to deliver drugs across natural barriers, such as the vessel wall or tumor cell membranes. In this regard, sonoporation induced by ultrasound-guided microbubble (USMB) destruction has been widely investigated in the enhancement of therapeutic drug delivery given it can help overcome these natural barriers, thereby increasing drug delivery into cancer.

High-risk types of human papillomavirus (HPV), such as HPV16, have been found in nearly all cases of cervical cancer. Therapies targeted at blocking the HPV16 E6 protein and its deleterious effects on the tumor suppressor pathways of the cell can reverse the malignant phenotype of affected keratinocytes while sparing uninfected cells. Through a strong interdisciplinary collaboration between engineering and biology, a novel, non-invasive intracellular delivery method for the HPV16 E6 antibody, F127-6G6, was developed. The method employs high-intensity focused ultrasound (HIFU) in combination with microbubbles, in a process known as sonoporation. Melissa Togtema *et al.* first demonstrated that sonoporation antibody delivery into the HPV16-positive cervical carcinoma-derived cell lines CaSki and SiHa was possible, using chemical transfection as a baseline for comparison. Delivery of the E6 antibody using sonoporation significantly restored p53 expression in these cells, indicating that the antibody is able to enter the cells and remains active.[6]

Role of sonoporation in head-and-neck cancer

Okunaga *et al*. conducted a study to examine the effect of ultrasound on oncolytic herpes simplex virus type-1 (HSV-1) infection in oral squamous cell carcinoma (SCC). Human SCC cell line SAS and oncolytic HSV-1 RH2, which was deficient in the neurovirulent γ134.5 gene and exhibited cell fusion actions, were used. Cells grown in multiwell plates were infected with HSV-1 and exposed to ultrasound in the presence or absence of microbubbles after an adsorption period. They found that tumor growth was suppressed with HSV-1 RH2 in combination with ultrasound, especially with microbubbles. The results indicated that ultrasound increased the efficiency of the HSV-1 infection in SAS cells and nude mouse tumors. The method can potentially be useful to enhance the antitumor effects of oncolytic HSV-1 on head-and-neck cancer treatment.[7]

Iwanga *et al*. in Japan studied the efficiency of sonoporation toward growth inhibition of human gingival squamous carcinoma cells *in vitro* and *in vivo*. The Ca9-22, a human gingival squamous carcinoma cell line, was used in the study. Sonoporation was used to deliver bleomycin (BLM) and transfect a cdtB-expressing plasmid into Ca9-22 cells *in vitro* and *in vivo*. The results showed that tumors nearly disappeared in Ca9-22 cell-implanted treated with BLM or cdtB expressing plasmid during the 4-week experimental period.[3]

Takagi Hironobu *et al*. administered a low dose of BLM by sonoporation with the anti-EGFR antibody producing a marked growth inhibition of Ca9-22 cells *in vitro*.[8]

In the current era, the foremost encounter in the management of HNSCC patients today is the expansion of the elusive cancer cell resistance to conventional approaches which has been overcome by drug delivery systems for the administration of chemotherapeutic agents. Various other modalities have certain limitations such as surgical resection, which leads to permanent disfigurement, altered sense of self and incapacitating physiological significances, while chemo- and radio-therapies result in significant toxicities, all upsetting patient welfare and quality of life. Thus, the advancement of novel therapeutic tactics or alterations of contemporary approaches is required which can be rectified by introducing targeted drug delivery systems and ultrasound-mediated devastation of microbubbles, which has been anticipated as a pioneering non-invasive drug delivery system for cancer therapy.

To conclude, in arrival of several new and advanced technologies, ultrasound-facilitated sonoporation aids as a bonus in therapeutic dentistry due to its non-invasiveness and simplicity which has made it superior to other methods. Literature indicates that sonoporation makes it possible to administer drugs into cells more efficiently and specifically, suggesting a novel application for the treatment of oral SCC. It could be considered as a forthcoming modality in the therapeutic field of medicine and dentistry.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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