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Optimal dose-response relationship in electrolytic ablation of tumors with a one-probe-two-electrode device

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ABSTRACT

Electrolytic ablation (EA), a medical treatment used in solid tumor ablation due to its minimum side effects and low cost, consists in the passage of a low constant electric current through two or more electrodes inserted in the tissue thus inducing pH fronts that produce tumor necrosis. Combined with a recently introduced one-probe two electrode device (OPTED) this procedure results in a minimally invasive treatment. Despite its success, EA has drawbacks such as the difficulties in determining the optimum dose-response relationship between the applied current, treatment time and necrotized tumor volume (NTV) and choosing a reliable dose parameter. In this work, a theoretical model is introduced describing the EA/OPTED as an electrolytic process and the underlying electrochemical reactions through the Nernst-Planck equations for ion transport. Model results show that the coulomb dosage is a reliable dose parameter and predicts an optimal dose-response relationship for a given tumor size subjected to an EA/OPTED, considering the optimum as the minimum coulomb dosage necessary to achieve total tumor destruction while minimizing healthy tissue damage. Moreover, it predicts a nonlinear relationship between coulomb dosage and NTV, dosage and NTV scaling as $Q^{1.4}$. Consequently, these results could have a significant impact on dose planning methodology aimed at improving the effectiveness of the electrolytic ablation.

1. Introduction

Electrolytic ablation (EA) of tumors, also called electrochemical treatment of tumors (EChT), is a non-thermal ablative method consisting in the application of a low direct electric current through two or more electrodes inserted in the tissue generating electrolytic products that induces tumor necrosis. This treatment was pioneered by Nordenström [1,2] and has been widely used in China with good clinical results [3,4]. In [5–8] the effects of EA in tumors in mice, either alone or with the use of chemotherapy, were studied. During the last decade, pulsed electric fields were explored in local tumor treatment based upon electroporation (EP), a technique in which pulsed electric fields are employed to perturb cell membrane permeability. Among them, electrochemotherapy (ECT) combines reversible EP with poorly-permeant anticancer drugs to potentiate their entry to the cell thus their intrinsic cytotoxicity. Since its beginnings in the late 1980s, ECT has evolved into a clinically verified efficient treatment for tumors of different origin in Europe [9,10]. Recently, in [11] it was shown that combining EA with reversible EP yields a significant increase in the extent of tissue ablation in comparison to that obtained with EA alone. A possible explanation is that reversible EP potentiates the entrance of toxic electrolytic products into the cell increasing NTV. NTV is defined as the volume of the tumor necrotized by EA. In summary, whether alone or combined with EP, some of the advantages of EA are its simplicity, effectiveness, and negligible side effects.

Tissue destruction in EA is mainly produced by necrosis. This is because, during the electrolysis process, electrochemical reactions take place at the electrodes, producing at the anode oxygen, chlorine and protons as the main byproducts, while hydrogen and hydroxide ions are released at the cathode.

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It is the presence of strong pH changes that causes necrosis. Concomitantly, there is a migration displacement of water from the anode to the cathode causing dryness at the former and hydration at the latter. Part of the gasses released at the electrodes remain present in the medium and participate in other chemical reactions with organic and inorganic components of the tissue [12].

In spite of the wide clinical experience available, still there is a need for a deeper understanding of the fundamental mechanisms involved in EA. Mathematical modeling validated with experimental measurements can greatly contribute to this goal. In a pioneering series of papers [12–16], *in silico* modeling of an EA protocol applied to a tumor tissue were presented. The tissue matrix was seen as an electrolyte and the EA protocol as an electrolysis process. The ion transport in a zone near one of the electrodes (cathode or anode) was described by a quasi-three-dimensional model (spherical symmetry model) using the Nernst-Planck equations for ion transport. Results show pH profiles at the anode to be strongly correlated with the size of *in vitro* measured necrosis, thus confirming the effect of pH (the spreading of hydroxyl ions) in tissue necrosis and suggesting that the model could be used for predicting EA tumor treatment. More realistic models were presented in [17] and [18] solving the one-dimensional Nernst-Planck equations for ion transport in which the full cathode-anode ion transport interaction was described. Results show that under EA modeling with two electrodes (with a separation of 3 cm between them), an initial condition with almost neutral pH evolves between electrodes into extreme cathodic alkaline and anodic acidic fronts moving towards each other, leaving the possible existence of a biological pH region between them; towards the periphery, the pH decays to its neutral values. Moreover, results also suggested that since necrotic areas correlated well with those covered by alkaline and acid fronts advances, pH front tracking can be effectively used to predict the extent of tumor destruction and thus, the assessment of EA effectiveness.

In [19] a one-probe two-electrode device (OPTED) containing the cathode and the anode very close to each other ($10^{-3}m$) was introduced; its main advantage under an EA protocol is the insertion of one applicator rather than two or more, thus minimizing tissue intrusion. Experiments show that upon application of the EA/OPTED protocols in a 3D gel model, two half-spherical pH fronts, one basic and the other acid (from cathode and anode, respectively), expand towards the periphery configuring a distorted full sphere. Between electrodes, the fronts collide and vanish due to neutralization. The efficacy of the EA/OPTED protocol was assessed measuring the extent of the necrotized area. This was determined by the area covered by acid fronts through a pH front tracking using pH color change indicators.

Dose planning methodology is mandatory for a reliable treatment outcome. Since the late seventies coulomb dosage (defined as the electric charge, that is, the intensity of the constant electric current applied multiplied by the time of its application) according to tumor size was the guideline for optimal choice of electric parameters [20]. Later on, searching for optimal dose planning, several authors investigated the dose-response relationship between the applied current, treatment time, coulomb dosage and NTV. Some authors [20] used different coulomb dosages and found a linear relationship between NTV and coulomb dosage (this was also experimentally corroborated in [17] though this result was not checked with a theoretical model). They also found no differences using lower or higher currents at a given coulomb dosage. Though these results seem to imply that coulomb dosage is a reliable parameter other authors [20] found NTV to be related, not only to coulomb dosage but also to the way at which it was administered. Low current and longer treatment times yielded higher NTV, compared with higher current and shorter treatment time [21]. Given these controversial results, the problem as to whether the coulomb dosage is a reliable dose parameter remains open.

The goal of this work is to establish the coulomb dosage as a reliable dose parameter and to determine the optimal dose-response relationship for a given tumor size subject to an EA/OPTED, that is, the coulomb dosage necessary to achieve total NTV while minimizing healthy tissue damage. This is obtained through mathematical modeling validated with experimental measurements.

The plan of the paper follows: Section 2, Material and methods, presents *In vitro* modeling and *In silico* modeling, Section 3, presents results of *in vitro* modeling and *in silico* modeling and a comparison between them and discussions, finally Section 4, presents general conclusions.

2. Materials and methods

2.1. In vitro *modeling*

In vitro modeling of the EA/OPTED protocol in a 3D gel cube is described in detail in [19]. Here we present a summary. As shown in Fig. 1(a) the tissue is represented by a gel cube ($0.023\ m \times 0.023\ m \times 0.018\ m$) consisting of 1% agar-agar in distilled water, with *NaCl* at physiological concentration ($160\ mol/m^3$). The OPTED is composed of two parallel needles separated $10^{-3}m$ from each other, and encased in a truncated cone holder, whose top and bottom diameters are $2\ 10^{-3}m$ and $5\ 10^{-3}m$, respectively (the holder has a length slightly larger than half of the gel cube width). Each needle is electrically insulated except at the point where it is in contact with the gel, thus the electrode. Each electrode has an exposed area of $1.5\ 10^{-7}\ m^2$. The OPTED is inserted in the middle of the cube back face. In [19] a constant current (taking the values: $4\ 10^{-3}A$, $8\ 10^{-3}A$ and $10\ 10^{-3}A$) was applied during 1200 *s*. The applied voltage ranged from 3.9 V at $2\ 10^{-3}A$ to 5.1 *V* at $10^{-2}A$. pH front tracking was done via an optical absorption technique. Phenolphthalein ($C_{20}H_{14}O_4$, transition pH range 8.0 - 9.62) and methyl red ($C_{15}H_{16}N_3O_2Cl$, transition pH range 4.8 - 6.2) were used as basic and acid indicators, respectively. Electric current circulation between the two electrodes in an electrolyte produces bubbles. If the electrodes are close enough, bubbles between them act as an electric insulator, diminishing the effective area through which electric current flows and increasing the current density.

2.2. In silico *modeling*

EA/OPTED therapy is an evolutionary process determined by the products emerging from the electrolysis process, in particular, pH fronts which are the main cause of tissue destruction. During the process, all the variables intervening in the electrolysis and in the generation of electrolytic products are modified. Clearly, pH fronts, thus EA/OPTED therapy, is a highly nonlinear process strongly dependent in the transport of ions and in the electrochemical reactions taking place at the electrodes.

Accordingly, for the establishment of the coulomb dosage as a reliable dose parameter and for determining the optimal dose-response relationship for a given tumor size subject to an EA/OPTED, the following *in silico* model describing the underlying ion transport process is introduced.

Assuming that ion transport is solely governed by diffusion and migration the *in silico* EA/OPTED model in a 3D domain is described by the Nernst-Planck equations for the concentration of ions in a four component electrolyte where Butler-Volmer and electroneutrality conditions prevail. Thermal effects are not taken into account in our model because they are considered negligible vis-à-vis pH fronts effects. The model comprises four unknown variables: the concentrations of $B = H^+$, OH^-, Cl^-, Na^+ ions. In passing, it is worth