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Quantification and Controllability Study of Minimally Invasive Exothermic Chemo-ablation Therapy for Tumor Ablation

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Abstract—**The recently proposed exothermic chemical reaction based tumor hyperthermia method presented a new way of realizing truly minimally invasive treatment for tumor. This method utilizes heat generated from the reaction between acid and alkali solutions to allow for tumor ablation. Successful clinical implementation of this method requires a clearer understanding and quantification of the ablation area such that a more controllable operation can be made. A number of in-vitro and in-vivo experiments are designed to examine the features of thermal chemo-ablation therapy which include micro and macro characteristics of ablated tissue and temperature change during the ablation process. A Quantitative study on the relationship between velocity and ablation volume as well as a Graphical User Interface in Matlab for computerized ablation area analysis are also presented in this article. We present in here two instrument designs for thermal chemo-ablation and have completed the prototype design for the injection pump which has been tested and successfully applied in ex-vivo and vivo experiments.**

I. Introduction

Most ablation therapies are thermal or chemical based. Thermotherapy has long been an important cancer treatment modality in which tumor tissue is exposed to an increased or decreased temperature to destroy cancerous cells. Compared to surgical resection, radiotherapy or chemotherapy, this therapy induces minor side effects so that it could be called a ‘‘green’’ therapy [1]. The chemical ablation process has an intuitive difference from the normal thermotherapy in that it uses chemical substances such as alcohol, acid, or alkali which destroy tumor cells due to protein coagulation and degeneration. Compared to thermal ablation therapy, devices for chemical ablation therapy is less complicated and easy to access. Syringes for routine use, analytical purity reagents and image-guidance are essential. Hence, the treatment cost can be greatly reduced. However, the toxicity of ablation reagents may affect normal functions of liver and kidney. In this article, a new way for ablation, the “thermal chemo-therapy” is introduced which combines thermal and chemical ablation methods and takes advantages of them In this method, acid and alkali solutions are delivered directly to the tumor tissue react, release heat and destroy tumor cells.. This method not only retains the coagulation mechanism in chemical ablation, but also generates tremendous amount of heat that is sufficient to increase temperature above the tissue-thermally-lethal threshold value, which is usually 45°C for tumor tissue. In addition, the reaction product is completely nontoxic for the human body. Since this therapy greatly eliminates or reduces the residual toxicity of reagents to the body, it meets the requirement for "green therapy". It has been recently proposed in another article by our group [2]. In order to improve the control ability during the procedure the quantitative relationship between ablation size and agent volume is required for. In this study, Therefore，we attempt to investigate the feasibility of this method through a series of ex-vivo procine liver experiments[3]-[20].

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II. Controllable Design of Thermo Chemo-ablation Therapy System

A. Clinical significance

The thermal chemo-ablation therapy requires percutaneous puncture which is accompanied by medical imaging modalities such as ultrasound to provide procedure guidance. For instance, by scanning the injection site, drug distribution can be monitored such that the injection process can be adjusted accordingly. However, due to the lack of automatic prediction of lesion size by machine, most of these operations are dependent on doctor’s experience (figure1).

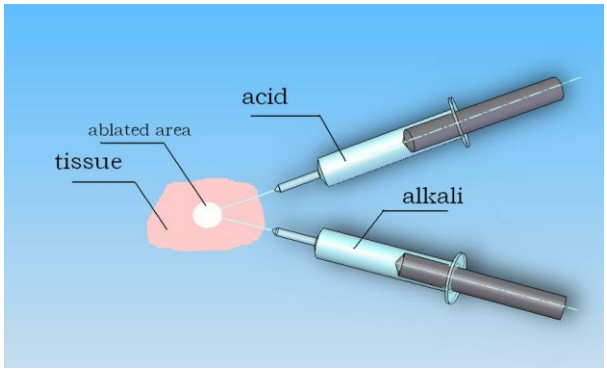


Fig. 1. Schematic of the hand operation of the thermal chemo-ablation therapy.

In pursuit of high-performance, minimally invasive cancer

surgery, the development of precise and controllable digital devices for the micro-injection is imperative. However, traditional piston pumps have fixed injection speed while some ablation reagents are corrosive to the transfer tube. All of these factors render the traditional equipment undesirable and obsolete.

B. Design

Here, we present a new controllable digital device for thermal chemo-ablation therapy.

In order to perform an ideal thermotherapy treatment using exothermic chemical reaction, there are some design limitations and considerations

a. Due to the strong corrosive nature of the chemical reagents, they should be safely isolated from the main system.

b. Solution flow should be continuous and the velocity should be adjustable.

c. The two streams of reacting solutions should reach the targeted ablation area simultaneously.

d. A control system should be incorporated to adjust the outflow of liquid.

Based on the above design requirements, our system consists of a control core, display and output modules, signal acquisition and processing modules, a stepper motor, a peristaltic pump and other auxiliary injection materials.

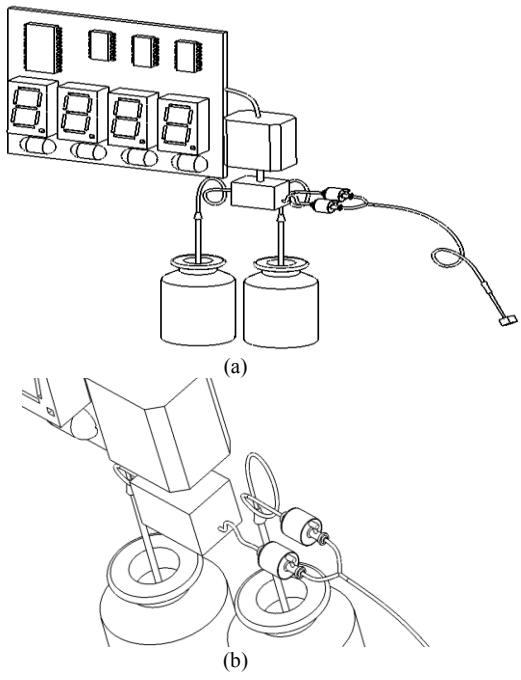


Fig. 2. Schematic of a device for controlled delivery of hydrochloric acid and sodium hydroxide solution. (a) Overall profile; (b) Device in detail.

Figure 2 shows the schematic drawing of a device used for the controlled delivery of hydrochloric acid and sodium hydroxide solution. During a thermo-chemical ablation procedure, the operator uses a keyboard to control the outflow velocity of liquids. The start and stop buttons allow the operator to manually control the operation process by changing the flow rate of the peristaltic pump in real time. The display module shows current flow rate and Feedback from sensors (local temperature or PH value). The high threshold of sensor values is previously set in the single chip. Once the returned value goes above the threshold, an alarm will occur and the system will stop automatically.

The advantages of this design include: 1, the peristaltic pump, which is used as a power converter in the chemical tumor ablation therapy, can precisely adjust the flow rate motors to improve the controllability of the procedure. 2, the transmission of corrosive solutions, only flow through sealed tubes which makes the operation process more reliable and safe. After the operation, only the tubes and sensors need to be sanitized. The entire device has very low maintenance cost because the peristaltic pump can be repeatedly used, and the patients only need to pay for the inexpensive ablation material. All of these factors can significantly reduce the cost of treatment. 3, the device can be used for multi-injection. 4, the use of thermocouple with glass package or pH sensor in this system as a feedback device, can provide quantitative information about physiological condition of the target tissue

III. Quantification Experiment Study

Since different chemical ablation reagents work based on different principles to destroy the extent of ablation result from each way is different. Fresh liver tissues in ex-vivo were separately injected ethanol, glacial acetic acid, 37.5% hydrochloric acid, 40% sodium hydroxide solution, and the combination of 37.5% hydrochloric acid and 40% sodium

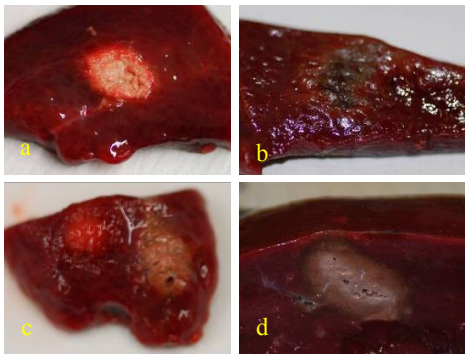


Fig.3. A variety of chemical and thermo-chemical ablation of the liver in vitro experimental results a. ethanol absolute b. glacial acetic acid c.40% sodium hydroxide (left area) on 37.5% hydrochloric acid (right area) ablation respectively, d.40% sodium hydroxide and 37.5% hydrochloric acid thermal chemo- ablation

hydroxide, respectively. Figure 3 shows the results of ablation by different chemical reagents. Differences of ablated tissue in gross pathology between each method are summarized in Table 1.The different ablated tissue forms under different ablation reagents were summarized in Table I. It shows that results from the thermo-chemical ablation method differ significantly from the traditional chemical ablation method. In particular, the color, porous and multilayered properties of the ablated tissue are varied. More importantly, the ablation

process involves in temperature change which appears differently for traditional chemo-ablation group and thermal chemo-ablation group. We recorded local temperature in tissue by using Agilent 3907A Data Acquisition Instrument with thermocouple sensors. Figure 4 shows the temperature change profiles of fresh liver under chemical ablation with 37.5% hydrochloric acid and thermal chemical ablation with 40% sodium hydroxide and 37.5% hydrochloric acid separately. The red curve illustrates a rapid temperature

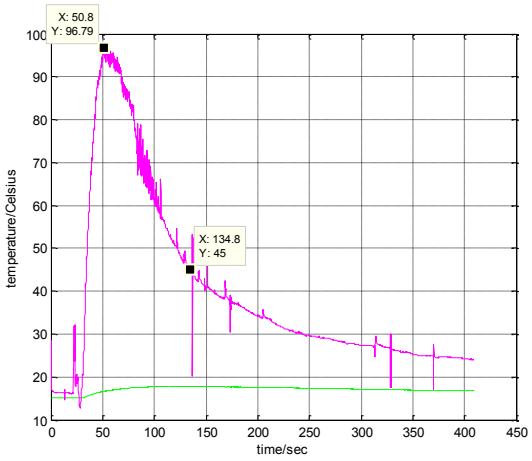


Fig.4. Temperature curves of the fresh liver under the chemical ablation with 37.5% hydrochloric acid and the thermal chemical ablation with 40% sodium hydroxide and 37.5% hydrochloric acid. The red curve stand for the temperature rapid buildup in neutrallzation reaction and the green curve stand for the stable temperature in the only chemical ablation.

buildup due to the neutralization reaction while the green curve shows a relatively more stable temperature profile when only chemical ablation is utilized. The thermo-chemical ablation can get much higher temperature (close to 100℃) at the center of injection , This is much higher than the tissue thermally lethal threshold value of 45℃.

The traditional chemical ablation in the clinical application assumes that the ablation area only depends on the reagent type and the volume of ablation reagent being used. It is also assumed that the diffusion profile of the reagents in the target tissue was spherical (usually unable to obtain the desired results). The empirical formula set up for the ethanol ablation is:

$$V = 3/4\pi(r+0.5)^3 \quad (1)$$

where r is the radius of the ablation tissue (ie, the size of target tumor), which unit is centimeters. And V is the volume of ethanol required, which unit is milliliter. The radius should increase to 0.5cm to ensure the total coverage of tumor ablation region. For the other types of chemical ablation reagents, such as glacial acetic acid, diluted hydrochloric acid, the formula should be multiplied by coefficients of 1 / 3 and 1 / 15 respectively, according to their varying penetrability [21]. The coefficient was obtained from experimental studies which had shown that acetic acid and hydrochloric acid had relatively stronger ablation ability than ethanol absolute.

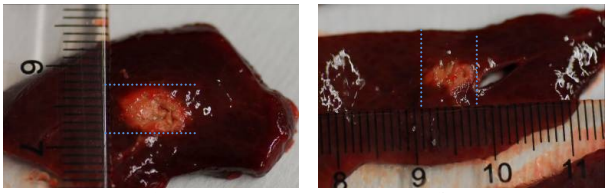
However, in practice, it was found that the ablation process was also dependent on the injection velocity (time), either in chemical ablation or thermo-chemical ablation, even when the volume of injection was same. Figure 5(a) shows the result of the ethanol ablation experiment using peristaltic pump at a rate of 0.25ml/min with an injection duration of 2 min, in which the largest longitudinal section was obtained. Figure 5(b) shows the result of experiment at a rate of 0.25ml/min with an injection duration of 8 min. We adjusted the two pictures using a standard 2-foot map to the same magnification. In the two experiments, the volumes of percutaneous ethanol injection are controlled to be the same, which is about 0.5ml. However we can read from the scale that the ablation areas of two-timed injection are $10\times6mm^2$ and $7\times3mm^2$ respectively. The differences in injection rates could lead to significantly different amount of coverage area by ablation. Thus, the study of the relationship between ablation area and the injection rate is a further step in working towards clinical application.

To further quantify the parameters in this method, the experiments of ethanol absolute ablation using peristaltic pump system to inject, respectively, at the flow rate of 0.2, 0.4, 0.8 and 1.6 ml/min were studied. After the experiments, the tissues were frozen at -18 ℃ for one hour, then cut into 2mm squares and then the maximum diameters of ablation regions were measured. The thickness of ablation regions was calculated by recording the number of layers.

Figure 6 shows the curve of different flow volume (calculated by the cuboid) against time. The result shows that the ablation area varied with ablation time and the rate of variety got more and more fast following the increase of the flow velocity.

TABLE I
COMPARE OF THE FORM OF TISSUES UNDER DIFFERENT ABLATION THERAPYS

Ablation reagents	Color of ablation tissues	Form of ablation tissue
ethanol absolute	white and sanguinity around	circular
glacial acetic acid	dust color	irregular
37.5% hydrochloric acid	off-white, having opaque area	circular
40% sodium hydroxide	red	quasi-circular
37.5% hydrochloric acid & 40% sodium hydroxide	off-white coagulation in the central, having opaque area around	circular with pore

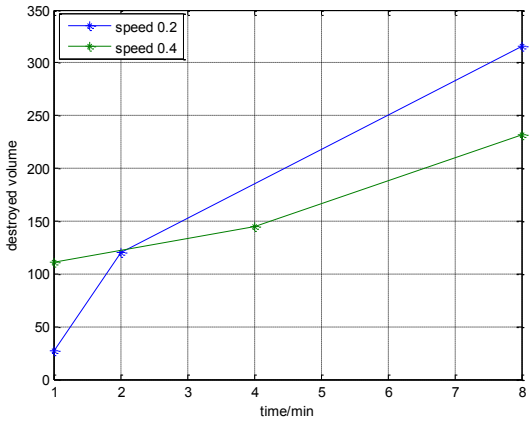


(a) (b)

Fig.5.(a) Picture of the result of the ethanol ablation experiment using peristaltic pump at a rate of 0.25ml/min injection in 2 min, (b) Picture of the result of the ethanol ablation experiment using peristaltic pump .at a rate of 0.25ml/min injection in 8 min.

IV. Discussion and Conclusion

The results from ex-vivo porcine liver experiments confirm



(a)

Fig.6. The relationship curve of different flow volume and the time at different flow speed.

that the thermal chemical ablation can create temperature high enough to kill the tumor tissue and meanwhile achieve the chemical ablation of target tumor tissue. A controllable thermal chemo-ablation therapy system was designed and assembled to meet the urgent need of clinical application. The results of the experiments also proved that the injection rate was one of the important factors in forming the ablation area. And we had proven that the rate of variety of the area ablation got faster following the increase of the flow speed.

Thermal chemical ablation combined with chemical and thermal ablation has many advantages such as minimally invasive, non-toxic and low cost. Therefore, this method has good prospects for clinical application. Moreover, it is expected that in the near future, such tumor treatment can possibly be performed on an outpatient basis based on the further research conducted about the controllability and the ablation monitoring technology.

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