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Image-guided Thermochemical Ablation: Theoretical and Practical Considerations

Erik N.K. Cressman

Abstract

***Purpose*: To test thermochemical ablation for potential as a new method to coagulate tissue and create a prototype device for administration.**

***Materials and Methods*: Reactions of either HCl or acetic acid and either NH_4OH or NaOH were run in triplicate in a gel phantom as a simple calorimeter. Data were recorded over a period of 5 minutes using concentrations from 1-12M in the case of HCl and NH_4OH. Comparison reactions were run at 11M using each acid reacted with each base. Two early device prototypes were devised using readily available components.**

***Results*: Maximum temperature rise was nearly instantaneous and was observed to peak with the 12M solutions at 106ºC. The maximum temperatures in the 11M comparisons were seen with the strong acid HCl paired with the strong base NaOH. The lowest temperatures were seen with the weak acid acetic acid paired with the weak base NH_4OH.**

***Conclusion*: Thermochemical ablation reactions can release adequate amounts of heat energy to cause tissue ablation.**

I. INTRODUCTION

One of the more common solid tumor targets for ablation is hepatocellular carcinoma. This disease is a leading cause of cancer mortality worldwide and carries a decidedly poor prognosis. Underlying the malignancy in many cases is end-stage liver disease which itself has a shortened life expectancy. In fact, hepatitis B virus (HBV)-related HCC is one of the leading causes of death due to cancer. Vaccination programs are showing signs of success in prevention but there are many parts of the world where the vaccine is not available in sufficient quantity. Here in this country [1] alcoholic cirrhosis and hepatitis C virus (HCV) infection are the most common causes. Prevention and eradication would be ideal, but there are no vaccines for HCV or alcoholism. The long latency period of HCC in the hepatitis C population from the 1980's and early 1990's means there is an wave of patients [2] that have begun to present clinically and will continue to do so for the next 10-20 years. Surveillance of patients at risk has been only modestly successful due to the low sensitivity of screening tests, the cost of repeated imaging studies, and the aggressive nature of the disease. Patients can go from showing no signs of malignancy to being inoperable all too frequently. In addition, an unknown but sizeable percentage of the overweight population is expected to contribute an increasing fraction of the patient population due to cirrhosis from fatty liver-related nonalcoholic steatohepatosis. Hepatocellular carcinoma is thus a growing problem and current therapies leave much to be desired.

Both a position statement by the Society of Interventional Radiology [3] and guidelines for quality improvement [4] have recently been published. Choice of treatment depends on severity of underlying liver disease, size and number of lesions, location of lesions, ability to detect them with MRI, non-contrast CT, or ultrasound, and local expertise. Many methods of tumor treatment exist outside the worlds of intravenous chemotherapy and surgery. A general way to divide these is into physical, chemical, and hybrid methods. Hyperthermia and cryoablation are two general physical methods and much work has been done to understand the mechanistic details of heat transfer, injury, the immune response, and ways to augment the size or durability of the treatments. Physicians currently use [5] RFA or less commonly microwave ablation to destroy a tumor with heat, combine heating with coadministration of liposomes containing drug, cryoablation to freeze a tumor, hepatic arterial drug infusion, bland arterial embolization, [6] chemotherapy combined with arterial embolization, drug-eluting bead for embolizations, selective internal radioembolization using radioactive labeled iodized oil [7] or radioactive microspheres as the embolic agent, external beam radiation therapy, or direct injection of ethanol [8,9] or acetic acid using ultrasound or other guidance [10] to ablate the tumor. Hot saline, boiling solutions of chemotherapy, and dilute sodium hydroxide [11] have also been studied but have not been widely accepted. Newer experimental methods involve electrolysis, magnetic targeting, magnetic resonance heating, antibody-drug targeting, various forms of nanotechnology, irreversible electroporation and high intensity focused ultrasound to name a few. Obtaining data from randomized controlled clinical trials in this setting is extremely difficult [12,13]and even *within* a particular method, there are no standardized protocols upon which to rely. Limitations of cost, side effects, incomplete treatment, and risks inherent to the procedures are accepted [14] because there is no truly effective treatment.

Among the lowest-cost and least-invasive methods is ultrasound guided percutaneous injection of either ethanol or acetic acid. These agents have been used primarily in Europe and Asia but suffer from the requirements for multiple treatment sessions because of local recurrence and toxicity concerns that limit dosing. Both treatments do allow for very localized tissue destruction, preserving liver tissue in the setting of marginal liver function. Given the

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Erik Cressman is with the University of Minnesota Medical School, Minneapolis, MN, 55455 USA (email: cress013@umn.edu).

systemic toxicity of ethanol or acetic acid which limits the dose, smaller tumors are more easily treated than larger or multiple tumors. In addition, tracking of injected agents along the paths of least resistance leads to a lack of predictability in the three-dimensional configuration of the ablation zone. An additional limitation for acetic acid is that the acid load can lead to hemolysis and renal failure if too much becomes intravascular. Tubiana et al [15] addressed the distribution issue with their technique in which contrast was added to the acid and the ablation performed under CT guidance to monitor for vascular leakage. Early investigations [16] of MR contrast agents show they are stable in ethanol and potentially suitable for MR-guided interventions. [17] An advantage of chemical ablation compared to a purely thermal method such as RFA is a decreased susceptibility to the heat sink phenomenon that leads to tumor recurrence near larger blood vessels. A recent study in China [18] of 187 patients comparing ethanol and acetic acid with radiofrequency ablation (RFA) suggested that RFA was somewhat more effective than chemical ablation but had a higher complication rate. Given the pressures on healthcare costs, it appears that there is an opportunity for comparably effective yet less costly treatment methods. One possibility to address this is the release of heat energy by carefully chosen chemical reactions, a method that has been termed thermochemical ablation. In order to deliver such a therapy, a new device would be needed to provide percutaneous image-guided access and at the same time constrain the reagents so that they did not react until near or at a target lesion. It would be important that reaction would occur quickly and completely so as to minimize exposure to unreacted starting materials. Here we will discuss our results using simple acid-base chemistry in a gel phantom, thermodynamic factors, and prototype device design considerations.

II. MATERIALS AND METHODS

Calorimetry

Commercially available baby oil gel (Johnson & Johnson or generic) was used for calorimetry experiments. This is composed of a mineral oil base with small amounts of a hydrogenated butylene/ethylene/styrene copolymer and a hydrogenated ethylene/propylene/styrene branched copolymer to increase the viscosity. It was dispensed in small portions into T25 culture flasks (Fisher Scientific, Chicago, IL, USA) for each experiment.

Acetic acid, hydrochloric acid, NaOH, NH_4OH, and Congo red pH indicator were purchased and used as supplied from Fisher Scientific. A thermocouple probe (Physitemp type T MT-29/1, Physitemp Instruments, Clifton, NJ, USA) positioned at the injection point allowed temperature data collection at completion of injection and every 15 seconds for 5 minutes using a T-type thermocouple thermometer (Digi-Sense, Cole-Parmer Instrument Co., Vernon Hills, IL, USA).

Equimolar amounts of acid and base were sequentially hand-injected over 10-15 seconds in 1 ml aliquots to permit formation of a discrete aqueous reaction chamber within the hydrophobic medium. Simple needle/syringe combinations were used. The pH indicator, congo red, was included in the acid solution prior to use to visually assess the extent of the neutralization reaction and completeness of mixing. Injections were performed in triplicate and average temperatures for each time point are reported.

Prototype Devices

The 17/18G coaxial biopsy needle was obtained from (Temno, CA, USA). The rotary hemostatic valve (Tuohy-Borst), the 5F vascular introducer sheath, and the 4F centesis catheter were obtained from Merit Medical (South Jordan, Utah, USA). The 21 G Chiba needle was obtained from COOK (Bloomington, Indiana, USA). For ex vivo use the biopsy set was inserted to a depth of approximately 2 cm in tissue and the inner trocar was removed. The Chiba needle was inserted first through the rotary hemostatic valve and the combination was inserted coaxially (figure 1) into the biopsy cannula. The tip of the Chiba needle was positioned to be within approximately 1 cm of the tip of the cannula. Alternatively, after inserting a vascular introducer sheath into tissue, a centesis catheter was placed through the hemostatic valve of the vascular introducer sheath and likewise positioned with the tip within 1 cm of the end of the introducer sheath. (figure 2).

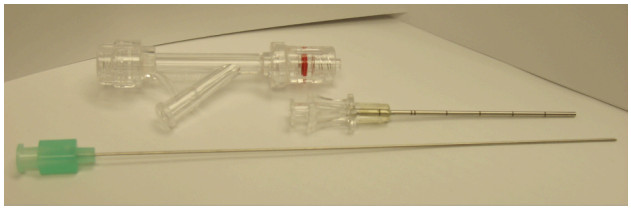

Figure 1: Components for a prototype of thermochemical ablation device. Tip of Chiba needle (green hub) is inserted through the rotary hemostatic valve which is connected to the cannula. The needle is then positioned to be still within the outer cannula to provide a mixing chamber during injection. Cost of parts is about $35.

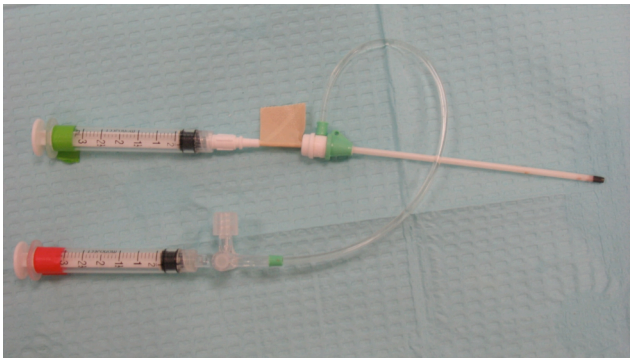

Figure 2: Plastic version of thermochemical ablation device that is MR compatible. The marker on the centrally placed centesis catheter (green syringe) is essentially a standoff to

maintain tip position within the sheath and provide a mixing chamber.

III. RESULTS

Effect of concentration on temperature

Figure 3 shows the data plotted for a representative series using HCl and NH_4OH as the acid and base. The maximum temperature was achieved within seconds after the completion of the injection in each case and the highest temperatures are seen at the highest tested concentrations. Temperature decay is rapid, in many cases approaching baseline within the observation period.

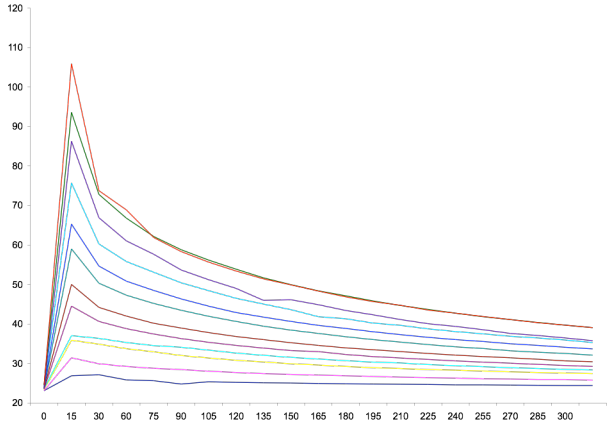

Figure 3: Plot for representative reaction between HCl and NH_4OH at increasing concentrations from 1 to 12M . Y axis is temperature (20-120 ºC) and X axis is time in seconds to 5 minutes.

Effect of acid and base strength on temperature

Table 1 shows a comparison of temperature among pairings of weak acid and base (acetic acid and NH_4OH) and strong acid and base (HCl and NaOH) at a concentration of 11 M. The lowest temperature is seen with acetic acid and NH_4OH and the highest temperature is seen with hydrochloric acid and NaOH. Values for the mixed combinations are in between these two extremes.

Reagent	HCl (s)	Acetic Acid (w)
NaOH (s)	105 ºC	74ºC
NH_4OH (w)	94ºC	59ºC

Table 1: Grid with maximum temperatures obtained in reactions of strong and weak acids and bases (s= strong, w= weak). Reactions were run at 11M.

IV. DISCUSSION

The molar heat of formation of water is on the order of 55 kJ/Mol for completely ionized (strong) acids and bases. This is not the case, however, for weak acids and bases. The rationale put forth in chemistry and chemical engineering literature is that some energy is lost to ionization of weak acids and bases prior to actual reaction. Generally accepted values for energy released from weak acids reacted with weak bases are in the range of 30 kJ/Mol. Intermediate values are seen with reactions between a strong acid and weak base or weak acid and strong base. The maximum temperatures seen were on the order of 105-110ºC and were seen with the highest concentration of the strong acid/strong base combination HCl and NaOH. The mixed pairings of acid and base resulted in temperatures bounded by the matched pairings. Somewhat unexpected, however, was that there would be as much variation as was seen and that the maximum temperature in the case of HCl and NH_4OH was as high as observed. This may be a reflection of the viscosity of NaOH as the concentration is increased. Above concentrations of 8-9 M the solutions of NaOH were noticeably thicker in character. The reaction rates themselves are nearly diffusion controlled so increasing the viscosity would impair rapid complete mixing. It is possible that the maximum temperature for HCl and NaOH should therefore actually be higher but that the current experiments are not adequate to obtain those data accurately.

It is generally accepted that at temperatures above 60ºC thermal coagulation necrosis in most tissues is rapid. The temperatures obtained in these experiments show that temperatures above that level are readily obtained. Less clear is the question of the duration of the exposure. In these experiments the injection of reagents, and hence the power input, is only on the order of seconds. This is much less than conventional radiofrequency or microwave ablation where the time window is at least several minutes and often significantly longer. The distribution of the injected material becomes more of a question as the volume is increased and this will affect the predictability of the shape of the resulting lesion. Most likely there will be a balance between volumes, injection rates, concentrations, and the particular salt products in such procedures that exists but remains to be found.

Choice of salt products could have profound effects through at least two different mechanisms. One is local cytotoxicity through denaturing effects, presumably predominantly through the anion component. This is well documented in biochemical literature for protein folding and stabilization as the Hofmeister series. A number of salts were ranked according to their tendency to promote unfolding (i.e. denaturation) of proteins. Thus in addition to heat as a denaturant, the products themselves will to some degree affect the protein structure and function.

Finally, there is the osmotic component. The physiologic milieu is in the range of 270-300 mOsm. The salt concentrations envisioned with thermochemical ablation will likely be at least one and approaching two orders of magnitude higher than this, at least at the center of an ablation. A gradient will be present as with the thermal lesion but this gradient is expected to persist much longer than the thermal excursion.

The devices themselves represent early attempts to create equipment that minimally fulfills the requirements for

injection from off-the-shelf parts. Among those requirements are configurations that provide capability for percutaneous access, a small diameter, low cost, availability, and prevention of mixing until at or near the tip of the device. Compatibility for use with MRI is an advantage of the plastic version but is offset currently by larger size and difficulty with distance from the tip of the sheath to the tapered stiffener tip. This creates an unwanted cavity and the tissues are more prone to fracture under such circumstances. In both models multiple pieces must be assembled. For true MR compatibility a compatible metal trocar or a significantly stiffened non-metal introducer would be required.

Limitations of this study include the lack of in vivo data and volume data. Also, the prototype devices do not provide complete mixing of reagents. The coaxial administration they provide predisposes to laminar flow given the fluid dynamics considerations. Studies are in progress to address these and other issues.

V. CONCLUSION

Thermochemical ablation has the potential to reach ablative temperatures in tissues. In addition, the byproducts of such reactions in most cases are cytotoxic in and of themselves due to both inherent denaturing characteristics of the salts and to the locally hyperosmolar concentrations produced. Much work remains to be done with regard to choice of acid and base, optimal concentrations, effects with altering stoichiometry, injection rates, and device optimization.

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