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Contrast Media–Doped Hydrodissection During Thermal Ablation: Optimizing Contrast Media Concentration for Improved Visibility on CT Images

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Abstract

OBJECTIVE—The purpose of this study is to determine a concentration of iodinated contrast media in saline and 5% dextrose in water (D5W) for organ hydrodissection, a technique used to physically separate and protect tissues adjacent to thermal ablations.

MATERIALS AND METHODS—A total of 28 samples were prepared from 1:1000–1:1 iohexol or iothalamate meglumine contrast media in either normal saline or D5W. Samples alone or juxtaposed with a homogeneous liver-mimicking phantom were imaged by CT using 80–120 kVp and 10–300 mAs. Mean CT numbers and noise were measured from the fluid, background air, phantom adjacent to the fluid, and phantom distant from the fluid. Visibility was determined from the contrast-to-noise ratio between the fluid and phantom, whereas streaking artifact was quantified by relative noise in the phantom. Measures were individually fit using multiple linear regression to determine an optimal contrast-to-fluid ratio for increased visualization without streaking. Contrast media– and blood-doped saline and D5W were also tested to determine whether such doping altered their electrical conductivity.

RESULTS—Iohexol concentration most influenced CT number; volumetric ratios of 1:1000–1:1 produced 20 HU to over 3000 HU. CT numbers were weakly dependent on x-ray tube voltage, whereas contrast-to-noise ratio and streaking artifacts were somewhat dependent on tube output. An optimal ratio of iohexol in fluid was determined to be 1:50. There was no significant difference between the electrical impedances of doped and pure saline or D5W ($p > 0.5$, all cases).

CONCLUSION—A 1:50 ratio of iohexol in saline or D5W provides an optimal combination of increased visibility on CT without streaking artifacts.

Keywords

hydrodissection; interventional oncology; microwave ablation; radiofrequency ablation; thermal ablation

Thermal ablation continues to gain acceptance as an alternative to surgical resection for treating tumors in the lung, liver, kidney, and bone [1–6]. When performed percutaneously, thermal tumor ablation is less invasive than and can be beneficial for patients refractory to traditional surgical resection [7]. Although many methods of thermal ablation exist,

radiofrequency ablation (RFA) is currently the most widely used technique, with cryoablation, microwave, ultrasound, and laser all at various stages of development and clinical use [8].

Thermal ablation has been characterized by low complication rates and is considered safe for many applications. However, unintended thermal damage to vulnerable tissues adjacent to the ablation zone (e.g., bowel, adrenal gland, gallbladder, pancreas, diaphragm, and body wall) can result in complications, including bowel perforation, hypertensive crisis, cholecystitis, pancreatitis, reduced long-term quality of life, severe pain, and even death [9–13]. To prevent these complications, several techniques for displacing and protecting adjacent tissues have been developed and studied. Balloon catheter inflation can be effective but is relatively invasive, expensive, and technically challenging. Infusion of carbon dioxide gas also provides an insulating effect [14–16]. However, the use of gas precludes ultrasound guidance and monitoring because of its poor transmission of acoustic energy.

Hydrodissection has emerged as a common technique to protect adjacent tissues from thermal damage. During hydrodissection, fluid is infused between the target tissue and the adjacent vulnerable structure. The fluid creates a physical barrier between the zone of ablation and the neighboring tissue, which decreases heating of the vulnerable tissue. Hydrodissection can be performed with sterile water, 0.9% NaCl (saline), and 5% dextrose in water (D5W) [17–23]. Sterile water is a suboptimal choice because it can cause a potentially dangerous ion imbalance. Saline should be avoided for RFA because it is ionic and, hence, can propagate RFA electrical current into adjacent tissues. D5W is an excellent choice for hydrodissection because it is isoosmolar and nonionic and, thus, provides both a physical and electrical barrier [24, 25]. Common issues with hydrodissection include fluid migration and diffusion, which can compromise its protective effects, and difficulty in differentiating the fluid from adjacent structures, especially the bowel when imaged with CT, making assessment of its location and any migration during the procedure challenging [26].

We hypothesized that combining the hydrodissection fluid with iodinated contrast media would increase visibility of the fluid, providing better contrast between the fluid and anatomic structures, such as fluid-filled bowel, and thus improved assessment of the fluid's location and whether or not it will provide the desired protective effect. In fact, a recent study showed the clinical utility of such an approach [27]. However, excessive iodine concentrations can lead to beam-hardening artifacts and reduced image quality (Fig. 1). Because iodinated contrast media and blood are ionic, another concern is that the contrast media or any bleeding induced during fluid infusion could compromise the electrically protective effects of the fluid. Therefore, the purpose of this study was to determine the optimal concentration of iodinated contrast material in saline and D5W for hydrodissection and to determine whether such doping affects electrical conductivity.

Materials and Methods

Sample Preparation

A total of 28 serial dilutions of nonionic (iohexol, 300 mg/mL) and ionic (iothalamate meglumine, 282 mg/mL) contrast media in saline and D5W were performed. Each sample contained a volume of 100 mL. For each combination of contrast media and fluid, volumetric mixture ratios of 1:1, 1:10, 1:50, 1:100, 1:200, 1:500, and 1:1000 were used. Control samples of pure saline and D5W were also produced. A subset of these samples was used for each of the experiments described later in this article.

CT Number Characterization

The x-ray attenuation coefficients of each combination of iohexol-doped fluid and control samples was determined by CT. Samples were scanned on a 64-MDCT scanner (Discovery VCT, GE Healthcare). Images were acquired using tube voltages of 80 or 120 kVp and tube outputs of 10, 60, 90, 150, and 300 mAs to cover the spectrum of high- and low-dose scan protocols during imaging-guided interventions. Additional CT parameters included 512×512 pixels, FOV of 9.6 cm in diameter, 5-mm slice thickness, 1:1 helical pitch, and 0.5-second gantry rotation period. Samples were placed in two columns on the CT bed, with each column containing either saline or D5W samples and each row paired by iohexol concentration. All samples were scanned during a single acquisition.

Axial CT images were analyzed offline in DICOM format using ImageJ (version 1.43k, National Institutes of Health). CT numbers in Hounsfield units were collected from an approximately 4×5 -cm rectangular region of interest (ROI) in the center of each sample. The mean and SD of CT numbers in the ROI were recorded for additional analysis.

Fluid Visibility and Image Quality Analysis

A separate study was performed to quantify the attenuation of each sample fluid with respect to a normal liver tissue phantom and to evaluate the severity of streak artifacts caused by samples with high iodine concentration. Each 100-mL sample was poured into a thin plastic bag, which was juxtaposed with the abdominal block of a CT phantom (PH-1, Kyoto Kagaku), and was imaged using the same CT system described previously in this article. The phantom material is a homogeneous polyurethane block with specific gravity of 1.06. Again, 80- and 120-kVp tube voltages were tested, this time with 10-, 90-, and 150-mAs tube outputs. All other imaging parameters were as described previously in this article.

Axial CT images were again analyzed with ImageJ. Four rectangular ROIs were collected from each sample in the background air, the fluid immediately adjacent to the liver phantom, the liver phantom immediately adjacent to the fluid, and the liver phantom distant from the fluid (Fig. 2). Overall image noise was determined from the SD in the background air (ROI 1). Relative visibility of the fluid was quantified using the contrast-to-noise ratio (CNR) between the fluid and liver phantom. CNR was determined as the difference between mean CT numbers in the fluid (ROI 2) and in the liver phantom distant from the fluid (ROI 4) relative to the mean noise between both ROIs. ROI 4 was used to reduce the effect of streaking artifact on the CNR measurement.

Finally, streak artifacts were evaluated as the noise added into the liver phantom adjacent to the fluid with respect to the background image noise—that is, the ratio of the SD in ROI 3 to that in ROI 1. Overall, samples that provided a CT number of 100–200 HU were considered ideal for clinical implementation. Samples that produced the highest CNR under all imaging conditions without additional streaking noise were considered optimal.

Electrical Property Verification

Finally, the relative electrical impedances of ionic and nonionic contrast media-doped samples were determined. Additional dilutions 1:1000–1:1 of fresh porcine blood in saline and D5W were also tested to verify that such contamination would not substantially affect fluid performance. Electrical impedance was measured between two plate electrodes 2, 4, and 8.5 cm apart in a 100-mL bath of the sample fluid. Impedances were measured from 0 to 1000 Ω using the “impedance check” function on a clinical RFA generator at 480 kHz (CC-1, Valleylab). One plate electrode was connected to the reference port of the generator, with the other connected to the generator output. Impedances greater than 1000 Ω were irresolvable but were considered sufficiently high to indicate an electrically protective effect

[25]. Impedances were then compared with pure saline and D5W to determine the relative impact of each doping medium.

Statistical Analysis

Multiple linear regression was used to arrive at empirical models for CT number (in Hounsfield units), CNR, and streak noise as a function of the contrast medium concentration, tube voltage in kilovoltage, tube output in milliamperes, fluid type, and any interactions between each factor. Each response (CT number, CNR, and streak noise) was modeled separately. Contrast medium concentration was converted as a log (base e) to minimize the influence of outlying observations and to improve matrix conditioning. Zero-contrast control vials were modeled using a dummy indicator.

The modeling procedure was as follows. First, a baseline model was fitted with contrast medium concentration, its square, and the control indicator variable as the sole predictors according to exploratory plotting. Candidate terms for inclusion into the model were added iteratively, and, for each term, a likelihood ratio F test was used to determine whether model fit improved significantly relative to the degrees of freedom consumed in the expanded model. If p was less than 0.05, then the new term was added to the model. Candidate terms included log concentration terms, fluid type, tube voltage, tube output, and any related pairwise interactions between them. Residual plots were examined to assess the validity of model assumptions. Goodness of fit was assessed with the coefficient of determination (R^2). Statistical computations were performed using *R* (version 2.10.0, R Project for Statistical Computing).

Results

CT Number Characterization

As expected, iohexol concentration had the greatest influence on the CT number, which increased with contrast media concentration (Fig. 3). Tube voltage also provided a significant but relatively small improvement to the regression model, with CT numbers at 80 kVp slightly greater than those at 120 kVp because of the increased iodine sensitivity at lower tube voltages. Therefore, the final regression model obtained for CT number (in Hounsfield units [HU]) was calculated as follows:

$$\ln(HU+100)=A+B\ln(X)+C\ln(X)^2+D \bullet KVP \quad (1)$$

, where X denotes the volumetric concentration (percentage) of iohexol in fluid, and KVP denotes the tube voltage. The coefficients for each term were found to be $A = 10.19$, $B = 1.292$, $C = 0.08729$, and $D = -0.005562$. This model was in excellent agreement with the data, accounting for greater than 98% of the variance ($R^2 = 0.9884$; standard error [SE] = 0.0898; $p < 0.0001$).

We observed that dextrose solutions had a slightly higher density when compared with saline, but the fluid type factor did not add significantly to the regression model ($p = 0.7$). Likewise, minor effects of tube current and an interaction between tube current and tube voltage did not significantly improve the model ($p > 0.9$, all tests). On the basis of this model, a 1:50 ratio of iohexol in either saline or D5W is expected to create an approximately 200 HU fluid, which is near the target value.

Fluid Visibility and Image Quality Analysis

Because of increased mean CT number, CNR between contrast media-doped fluids and the liver phantom was also most influenced by iohexol concentration (Fig. 4). Unlike mean

signal intensity, CNR was not significantly related to tube voltage, but it was influenced by tube output. As a result, the final regression model for CNR was as follows:

$$\ln(\text{CNR})=A+B\ln(X)+C\ln(X)^2+D\sqrt[3]{MAS} \quad (2)$$

, where *MAS* is the tube output. The coefficients for each term after correcting the offset error in the liver phantom were $A = 1.607$, $B = 0.4854$, $C = 0.03560$, and $D = 0.3203$. This model was in excellent agreement with the data, accounting for greater than 93% of the variance ($R^2 = 0.9350$; $SE = 0.2351$; $p < 0.0001$).

Qualitatively, we noted very little streaking noise at iohexol concentrations below 1:10. Concentrations at or above 1:10 led to streaking, which increasingly negatively affected image quality in the liver phantom (Fig. 5). Quantitatively, the best-fit regression model for streak artifact (*SA*) was as follows:

$$\ln(\text{SA})=A+B\ln(X)+C\ln(X)^2+D\ln(X)^3 \quad (3)$$

, for $A = 0.7367$, $B = 0.1201$, $C = 0.06643$, and $D = 0.006853$. Unlike CT number and CNR, this model could account for only 59% of variance in the data ($R^2 = 0.5900$; $SE = 0.2511$; $p < 0.0001$). Additional terms related to tube voltage, tube output, and fluid with interactions among different sets of terms slightly improved the goodness of fit, but not significantly ($p > 0.1$, all tests).

Electrical Property Verification

We observed no significant differences between the electrical impedance at 480 kHz measured through nonionic iohexol in D5W samples, or ionic iothalamate meglumine samples in saline samples at or below the optimal concentration of 1:50 (Fig. 6; $p > 0.05$, all tests). As the volumetric ratio of contrast material increased, iohexol tended to decrease the impedance of saline samples, whereas iothalamate meglumine tended to decrease the impedance of D5W. The addition of blood to saline or D5W did not significantly affect fluid impedance ($p < 0.05$, all tests).

Discussion

This study determined that contrast-to-fluid mixture ratios of 1:50–1:100 are suitable to increase the visibility of hydrodissection fluids saline and D5W in the abdomen. Within this range, a 1:50 ratio appears to be optimal because it provides the greatest visibility on CT but does not produce substantial streaking noise. These mixture ratios are applicable for both low-dose and diagnostic CT parameters. Our findings suggest that the addition of iohexol to saline or D5W will lead to better visibility of the hydrodissection fluid and, thus, lead to clearer delineation of boundaries between soft-tissue structures at all stages of procedural targeting and monitoring without compromising the electrical and physical barrier that it creates. This should improve the already excellent safety profile of imaging-guided tumor ablation by ensuring that the hydrodissection fluid is providing an adequate barrier between the ablation zone and the surrounding vulnerable structures.

In addition, the study established that neither contrast media (nonionic 300 mg/mL iohexol and ionic 282 mg/mL iothalamate meglumine) nor blood significantly affected the electrical conductivity of the hydrodissection fluid in the 1:50–1:100 range. This finding was particularly important to verify the noninferiority of doped D5W as an electrical barrier for RFA. However, saline is inherently ionic, has high electrical conductivity, and should not be used as a protective measure during RFA, with or without contrast media [24, 25]. The

addition of nonionic contrast media did not substantially increase the electrical impedance of saline to confer any sort of practical benefit as an electrical barrier.

Multiple groups have reported the efficacy of hydrodissection during thermal ablation [17–23, 27]. Typical anatomic sites of injection include spaces between the liver or kidney and the diaphragm, body wall, bowel, pancreas, or stomach. Several hundred milliliters of typically normal saline or D5W are used to maintain a tissue separation of several millimeters. In most cases, the fluid is left in situ after injection and is absorbed within a few hours of the procedure. In combination with other techniques, such as biliary or ureteral stent placement and perfusion, hydrodissection has enabled more-aggressive patient selection for percutaneous ablation [23, 27, 28]. Before the use of these adjunctive techniques, tumors in locations adjacent to vulnerable structures may have necessitated a laparoscopic or open surgical approach, which is more invasive, more expensive, and technically more challenging [29]. Improved visualization of the fluid may enable more widespread use of hydrodissection, which may, in turn, reduce complications as a result of thermal ablation.

A previous report [27] has described the use of hydrodissection using contrast media–doped fluids and CT; however, that report did not systematically investigate the quantity of iohexol in the hydrodissection fluid. Air and carbon dioxide are also potential fluids that can be used for minimally invasive organ dissection, and they provide good contrast on CT with some abdominal structures. However, dissection gas is isodense on CT with intestinal gas and can be difficult to localize within the body cavity. Gas also precludes ultrasound imaging to guide applicator placement if it is present in the imaging window. A hydrodissection fluid doped with iodine-based contrast media provides positive CT contrast with both abdominal organs and intestinal gas but does not enhance ultrasound images.

A primary limitation of this study was its limited human subject data. Phantom models lack the natural variability in CT attenuation that exists in human subjects. Clinically, an obese patient will produce more x-ray attenuation and may require a slightly higher concentration of contrast agent to optimize the fluid–soft tissue contrast. However, because of the low influence of x-ray tube voltage or current in the selection of optimal contrast-to-fluid mixture ratio, we expect the 1:50 ratio to be suitable for most patients. The phantom model also did not allow evaluation of contrast agent absorption or its potential effect on renal function. However, we note that the ideal mixture ratio introduces only a small amount of iohexol (e.g., a 500-mL preparation using a 1:50 ratio contains 10 mL of iohexol). The clinical implications of this small amount of absorbed contrast agent are yet to be determined but, with the possible exception of a contrast agent allergy, are almost certainly negligible. This ratio is now used routinely at our institution with good results, as noted in Figure 1.

In conclusion, combining 300 mg/mL iohexol with saline or D5W can improve visualization of each hydrodissection fluid, with a contrast-to-fluid mixture ratio of 1:50 providing an optimal balance of increased contrast between the fluid and surrounding tissues with minimal beam-hardening artifacts. This should improve the precision of hydrodissection in clinical applications and thus allow an improvement in the safety profile of percutaneous imaging-guided ablation.

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Fig. 1.

Clinical examples of contrast media–doped hydrodissection in four different patients. Fluid is noted with asterisks. Without doping, 5% dextrose in water (D5W) appears nearly isodense with surrounding tissue structures, especially fluid-filled bowel. Iohexol-doped D5W is hyperdense and easier to visualize, but can create streaking artifacts if concentration of iohexol is too great (**A**).

A, 70-year-old man. Ratio of iohexol to D5W was 1:5, and mean CT number in fluid space was 750 HU.

B, 54-year-old man. Ratio of iohexol to D5W was 1:50, and mean CT number in fluid space was 135 HU.

C, 69-year-old man. Ratio of iohexol to D5W was 1:100, and mean CT number in fluid space was 90 HU.

D, 78-year-old woman. Ratio of iohexol to D5W was 0, and mean CT number in fluid space was 45 HU.

Fig. 2.
Sample CT phantom image with regions of interest (ROIs) identified.

Fig. 3. CT number versus iohexol concentration for all samples measured at 120 kVp (*black squares*) and 80 kVp (*gray diamonds*). Best-fit multiple linear regression models are also shown as dashed lines for each tube voltage. Note that CT numbers for 1:1 (50%) concentrations of iohexol in each fluid reached upper limit of values output by CT scanner.

Fig. 4. Contrast-to-noise ratio (CNR) for all samples at tube outputs of 10 mAs (*black squares*), 90 mAs (*gray diamonds*), and 300 mAs (*gray triangles*). Best-fit multiple linear regression models are noted as dashed lines for each tube output. Greater CNR is realized by both higher iohexol concentrations (because of much greater CT numbers) and higher tube outputs (because of lower image noise).

Fig. 5. Streaking artifact as ratio of noise in liver tissue phantom adjacent to hydrodissection fluid and background image noise. Streaking noise was not evident until iohexol concentration approached 10%.

Fig. 6.

Mean electrical impedance measured through samples of saline (*lower curves*) or 5% dextrose in water (D5W) (*upper curves*) with iohexol, ionic iothalamate meglumine, or blood. Impedances beyond 1000 Ω were not measurable. Volumetric ratios less than 1:10 (10%) were not associated with significant changes in fluid impedance, indicating that optimal concentration of 1:50 will not substantially change performance of pure saline or D5W.