MRI-Guided Electrochemotherapy (ECT) in a Rat Model of Hepatocellular Carcinoma

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INTRODUCTION

Electropermeabilization involves application of electrical pulses to increase cell membrane permeability; electrochemotherapy (ECT) takes advantage of this phenomenon to increase tumor uptake of chemotherapeutic drugs [1, 2]. The timing of drug infusion and application of electrical pulses is critical to optimize the ECT procedure [1]. The purpose of this study in rat hepatocellular carcinoma (HCC) model was to demonstrate the potential to use dynamic contrast-enhanced MRI for intra-procedural optimization and monitoring during intra-hepatic ECT.

METHOD

Animal Model 12 male Sprague Dawley (SD) rats (weighting 301-325g) were used for our ACUC-approved experiments. Each rat was double implanted with 1×10^6 N1-S1 rat HCC cells (ATCC, Manassas, VA) injected into the right lobe and left medial lobe, respectively. Two N1-S1 hepatomas were grown in ten rats. Hepatomas grown in the left lobe were treated with MRI-guided ECT, while the hepatoma in the right lobe was not electroporated (serving as internal control).

DCE-MRI All experiments were performed using a 1.5T clinical MR scanner (Espree, Siemens Medical Solutions). T2-weighted (T2W) TSE images were acquired to optimize imaging positions for subsequent DCE scans with the following parameters: TR/TE= 3640/56msec, slice thickness=5mm, Average=3, matrix size=192×120, turbo factor=7, bandwidth=205. A pre-treatment dynamic contrast enhanced MRI (DCE-MRI) was performed with an injection of Gd-DTPA through femoral vein with the following parameters: TR/TE=21/2.48msec, slice thickness=5mm, FA=20º, matrix=128×58, bandwidth =501Hz/pixel, 1sec/measurement and 80 measurements in total. A contrast enhancement curve was generated to estimate the time delay between bolus infusion and the period of maximum tumor uptake (used for planning purposes to optimize delay interval, Td, between later cisplatin infusion and application of electrical pulses). An immediate post-treatment DCE-MRI was performed to monitor the reduction in tumor perfusion due to ECT vascular lock effects [3].

ECT Procedures A BTX Electroporator (ECM830; Harvard apparatus, Holliston, MA) function generator and a parallel two-needle array were used. For ECT treated tumors, bi-polar electrodes (1cm spacing) were inserted straddling the targeted tumor and 8 100μs 1300V pulses applied at the selected delay interval T_d after the administration of cisplatin (Spectrum Chemical Corp., NJ) solution (4mg/kg dissolved in 1ml saline) through femoral vein [3].

ICP-MS Animals were euthanized 2 hours after treatment; both hepatoma and normal liver tissues were harvested and sectioned; inductively coupled plasma mass spectroscopy (ICP-MS) was used for intra-tumoral cisplatin drug concentration measurements to compare ECT to non-electroporated internal controls.

Statistical Analysis All statistics were performed using SPSS (SPSS, Chicago, IL). Platinum concentrations between ECT tumors and non-electroporated internal control tumors were compared with paired t-test ($p<0.05$ considered significant).

RESULTS

Post-ECT DCE-MRI measurements demonstrated reductions to perfusion (reduction in perfusion level and lack in perfusion peak) due to electrical pulses related vascular lock effects in electroporated tumor compared to the non-electroporated control tumors in each rat (Fig. 1**C**). ICP-MS analysis of platinum concentrations showed significant increases in cisplatin uptake in the ECT treated tumors compared to non-electroporated controls in eight rats (n= 8/10, 66% increase, P=0.002, Fig. 1**D**).

CONCLUSION

Our findings suggest that ECT permits superior chemotherapeutic drug uptake within targeted HCC compared to conventional chemotherapy in the N1-S1 rodent model. Dynamic contrast enhance MRI shows the potential to allow patient-specific adjustments to ECT timing parameters for optimal drug delivery to targeted hepatic tumors and monitoring of electroporation related vascular lock perfusion changes.

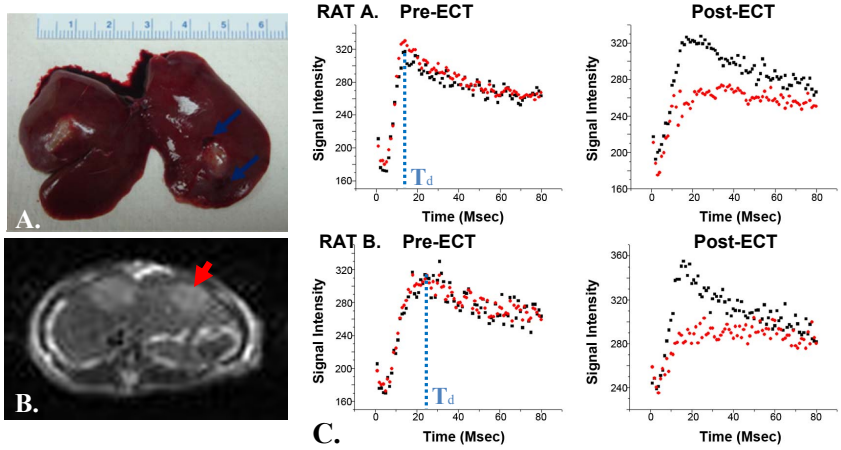

Fig. 1. (A). Gross image of a representative liver specimen (blue arrow, electrodes inserted positions) (**B**). T2-weighted images showing hyper-intense N1-S1 hepatoma (red arrow, tumor in left medial lobe treated with ECT) (**C**). DCE-MRI images generated tumor enhancement curves from two representative rats in rows before treatment (**left**) and after treatment (**right**), showing a reduction of perfusion after treatment in the ECT tumors (**red**) compared to the internal controls (**black**).

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