

Novel Delivery System for Minimally Invasive MR Guided Neurological Interventions

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Introduction

The delivery of electrodes or other therapeutic agents to the brain frequently requires precision minimally invasive access. MR is ideally suited to this application and high targeting accuracies have been reported when delivering deep brain stimulator (DBS) electrodes (1). Convection enhanced delivery (CED) is a promising technique for delivering drug and gene therapies to the brain (2). The technique uses continuous injection of a fluid containing the therapeutic agent and the positive fluid pressure actively convects the agent through the interstitial space. Thus, a point source infusion can be used to deliver the agent over volumes that encompass the targeted brain structures. This approach bypasses the blood brain barrier and allows the distribution of larger therapeutic agents that are unlikely to migrate significantly simply by diffusion. Intra-operative MR imaging has been used to monitor the delivery of therapeutic agents via CED (3), but with more invasive methods and limited targeting accuracy.

We have developed a second generation delivery platform (Figure 1) that is capable of inserting DBS electrodes or infusion cannula's for CED. We evaluate the targeting accuracy that can be achieved with this platform in phantoms and present its application to CED-based delivery in a primate model of Parkinson's disease.

Methods

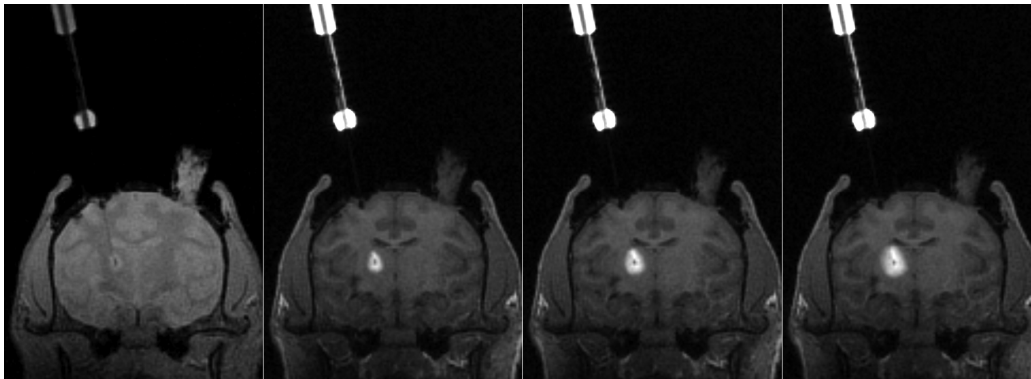
Targeting accuracy was initially tested in a skull phantom that was filled with gel and contained 8 discrete targets. Studies were performed on four different days by 3 separate surgeons. The same trajectory guide alignment strategy was applied in all cases and approximates that described in (1). Targeting accuracy (radial error) was assessed by the difference between the selected target and the resultant position of a rigid ceramic mandrel that was inserted into the phantom following trajectory guide alignment. This measurement was made in the same scan plan in which the target was selected and the magnitude and direction of error was determined.

A non human primate (NHP) animal model of Parkinson's disease was subsequently used to evaluate the delivery platform and to monitor CED infusions. Animal protocols were approved by our institutions animal care committee. Two NHP's were infused bilaterally on 2 separate occasions, for a total of 8 targeted CED infusions. Targeting accuracy was established based on the same criteria as the phantom study and the spatial distribution of a Gadolinium doped (1.0 mM) saline infusate was monitored for up to 60 minutes (infusion rates = 1.0–4.0 ul/min).

Results

Targeting accuracy in our phantom study was found to be 0.5+/-0.3 mm (range=0.0-0.9 mm). These results were obtained with a single penetration of the gel and with path lengths from the trajectory guide of 85-90mm. Accuracy was not affected by the surgeon performing the procedure and no consistent directionality to the error was detected.

CED infusions were successfully performed in all cases (Figure 2). Anatomical structures that were targeted included the putamen, thalamus and subthalamic nucleus. Target accuracy was comparable to phantom studies and infusion volumes extending up to 10mm in diameter were achieved in the target structures.



Conclusions

This newly developed delivery platform for precisely localizing neurological structures achieved very high targeting accuracy in phantom evaluations. This accuracy was reproduced in an NHP model and the administration of CED therapy was effectively demonstrated with this minimally invasive delivery approach.

References: (1) Martin,AJ et al., Magn Reson Med. 2005 Nov;54(5):1107-14. (2) Bobo,RH et al. Proc Natl Acad Sci U S A. 1994 Mar 15;91(6):2076-80. (3) Fiandaca,MS et al. Neuroimage. 2009 Aug;47 Suppl 2:T27-35.



Figure 1: The MR compatible trajectory guide developed for DBS placement and targeted infusion via CED. The guide has an MR visible alignment indicator that has a central lumen through which an electrode or cannula can be inserted. Its orientation can be manipulated around a pivot point and parallel trajectories can be performed with an X-Y translation stage.

Figure 2 – A CED infusion in an NHP is demonstrated. The external alignment indicator is manipulated until it projects to the selected target in the thalamus and the infusion cannula is inserted to the appropriate depth (left). T1-weighted (3 right images) are then used to monitor the volumetric coverage of this Gd-doped solution.