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Interventional MRI-guided catheter placement and real time drug delivery to the central nervous system

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Abstract

Local delivery of therapeutic agents into the brain has many advantages; however, the inability to predict, visualize and confirm the infusion into the intended target has been a major hurdle in its clinical development. Here, we describe the current workflow and application of the interventional MRI (iMRI) system for catheter placement and real time visualization of infusion. We have applied real time convection-enhanced delivery (CED) of therapeutic agents with iMRI across a number of different clinical trials settings in neuro-oncology and movement disorders. Ongoing developments and accumulating experience with the technique and technology of drug formulations, CED platforms, and iMRI systems will continue to make local therapeutic delivery into the brain more accurate, efficient, effective and safer.

Keywords

Interventional MRI; real time; catheter placement; convection enhanced delivery; drug delivery

Introduction

Local delivery of therapeutic agents into the central nervous system offers many advantages, including circumventing the blood–brain barrier, minimizing systemic toxicity, and potential for achieving higher concentrations of agents at the target site. Catheter based delivery systems were developed to achieve such goals, using minimally invasive entry sites to introduce infusion catheters into targets, including deep seated lesions. Because accuracy was of utmost importance, frame-based or frameless stereotaxis was utilized, with trajectories that were based on a host of planning platforms. From its early applications, it became evident that in addition to the safety and efficacy of the agents at the target sites, factors paramount to the success of these approaches included reliable targeting to ensure accurate catheter placement and understanding the pattern of distribution of the infusions.

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Convection-enhanced delivery (CED), utilizes continuous pressure gradient to distribute macromolecules into the interstitial spaces of the brain parenchyma. Preclinical and clinical development of CED showed promise given its capability to distribute the infusate into large volumes of tissue [1]. Despite success in early phase trials for its use in gliomas, large scale phase III experience with CED delivering IL13-pseudomonas exotoxin for recurrent glioblastoma was disappointing, failing to show clinical benefit in survival [2]. The investigators of the PRECISE trial describe the lack of knowledge of the infusion distribution as a major potential explanation for lack of efficacy. *Post hoc* analysis of the PRECISE trial patients revealed that more accurate catheter placement was correlated with larger distribution of the agent, but overall coverage of the tumor was low [3,4]. In addition, less than half of the implanted catheter were in optimal position, reflecting the difficulty of achieving such processes, and in fact only 68% of catheters were positioned in exact accordance with protocol guidelines in the trial [2,3]. CED has also been utilized for delivering adeno-associated virus serotype 2 (AAV2) carrying various genes of interest to the basal ganglia in patients with Parkinson's Disease (PD) [5–7]. After promising phase I studies, a phase 2 trial of neurotrophic therapy infusion yielded negative results, and lack of clinical benefit was felt to be largely due to inadequate vector delivery and poor target coverage [8].

Advancements in imaging and planning/targeting platforms have allowed for improved targeting, more accurate catheter placement, improved drug distribution, and real-time visualization of infusions. In addition, improvements in cannula design have resulted in more reliable, efficient, and increased distribution of agents [9]. These new image guided systems provide real-time visualization of the infusion using a gadolinium based co-infusate, allowing for real-time alteration of infusion parameters, such as flow rate, repositioning the catheter, or terminating the infusion if necessary [10,11]. One such system developed by our group is an integrated hardware/software system including new catheter design and targeting/infusion monitoring software platform, called ClearPoint (MRI Interventions, Irvine, CA). It was initially developed to improve the safety and accuracy of implanting deep brain stimulation (DBS) electrodes, and evaluation of targeting accuracy did seem to be enhanced compared to the existing commercial system at the time [10]. Here we review the current workflow and application of the interventional MRI (iMRI) system for catheter placement and real-time visualization of infusion using the ClearPoint navigation platform.

Setup and technique

The system includes the mounted cannula insertion guide (SmartFrame), the infusion cannula (SmartFlow) and targeting software system that integrates with the MRI console in the iMRI suite. First, the patient's head is fixed in an MRI compatible Mayfield fixation device attached to the MRI table (Figure 1). While most cases were performed in a supine position with up to 30 degrees of head turn allowable as needed, the prone position has also been successfully used by our team (Figure 1). The patient's head is then positioned at the isocenter of the scanner bore, and high resolution anatomical MR images are obtained for surgical planning and target acquisition. Then, a localizing adhesive grid (SmartGrid) is placed over the approximate region of the preplanned entry site, and another volumetric scan

obtained (Figure 2). The ClearPoint software generates an entry point within the SmartGrid, and a skull mounted or a scalp mounted SmartFrame is mounted over the marked entry site.

The SmartFrame has an infusion cannula guide, which contains a gadolinium impregnated fluid stem and fiducials allowing for automatic detection by the software (Figures 3 and 8). Detecting the fluid stem allows the software to guide the alignment of the cannula guide to the target trajectory through adjustments made on the X–Y translational and the pitch-roll axes by knobs built into the frame. These adjustments can also be made using hand controllers extending out to the opening of the MRI bore for easy access to the neurosurgeon (Figure 4). Serial images then can further guide refinements along the cannula guide stage until it matches the planned trajectory with the expected error <1.0 mm. The pitch and roll axes on the SmartFrame are locked and two-dimensional scans were acquired along the sagittal and coronal axes to guide fine adjustment of the cannula guide along the X–Y stage. The ClearPoint software generates further instructions for turning the knobs, and this process is repeated until the reported expected error fell below 0.5 mm.

A burr hole is then created, and if the scalp mounted frame is being used (Figure 5), a handheld twist drill along the planned trajectory using a guide bore can be used. The software also calculates the distance from the top of the guide stem to the target, and makes sure that infusion will not create a bore collision between the top of the catheter and the MRI bore when the patient is being scanned. A depth stop is secured at the distance along the catheter that ensures the catheter tip will end up in the target. We utilize a ceramic, fused silica catheter with a multistep tip to resist reflux [12]. The catheter is connected to a syringe mounted on a MRI compatible infusion pump away from the sterile field (Figure 6). The infusion is started at 1 $\mu\text{L}/\text{min}$ until fluid flow from the cannula tip could be visualized. The cannula is then advanced through the guide tube of the SmartFrame into the brain to the target depth. When the cannula is advanced to the depth stop, it is secured with a locking screw on the guide stem, and the infusion is started (Figure 7).

Repeated fast multiplanar T1 images are obtained every 5 min to visualize the infusion. The images are an in-plane resolution of $0.7 \times 0.7 \times 1$ mm with 128 slices over the 180 mm field of view. The infusion typically utilizes a gadolinium co-infusate to allow for real-time visualization of the delivery (Figure 8). Once the infusion is visualized at the catheter tip, the infusion rates can be increased to the rates determined by the specific study protocols. The system has been utilized successfully for both 1.5 and 3 Tesla scanners, and regular and wide bore scanners.

Expert commentary

At our institution, real-time CED with iMRI has been successfully applied and studied in a number of different clinical investigation settings. We believe that the ClearPoint system's integrated software/hardware setup allows for ease of entry point and trajectory planning, as well as accurate navigation to the target. For recurrent glioblastoma, an early phase trial of intratumoral CED of Toca 511 was just completed successfully (NCT01156584, clinicaltrials.gov). Toca 511 is a retroviral replicating vector containing the gene for cytosine deaminase, and by delivering the vector into the target tumor site, gene transfer occurs to the

tumor cells, allowing for prodrug activation of flucytosine into the antineoplastic drug 5-fluorouracil (5-FU) by the tumor cells. Co-infusion with gadoteridol allowed for real-time imaging, and in select cases infusion rates of up to 50 $\mu\text{L}/\text{min}$ were achieved safely without reflux. A phase I trial of real-time CED of nanoliposomal irinotecan (nano CPT-11) for recurrent glioblastoma is currently open for enrollment at our institution (NCT00734682). The delivery by CED of nanoliposomal formulation of irinotecan, an antineoplastic topoisomerase inhibitor, has undergone preclinical investigation by our group [13], and co-infusate of gadoteridol is again being used for real-time visualization. The dose escalation design of this trial will ultimately aim for treatment of tumors up to 6 cm^3 , with total infusion volumes of up to 2 ml and infusion rates of up to 50 $\mu\text{L}/\text{min}$. Both trials have been carried out in nearly two dozen total patients to date without any intraoperative complications, including no hemorrhages, and 90% of patients discharged from the hospital the morning of postoperative day one. The average total procedure time for the phase I CED of irinotecan has been 5 h, and the average infusion has been 1 h per 1 ml of infusion.

We also have an ongoing phase Ib trial using real-time CED and the ClearPoint platform to deliver AAV2 carrying a gene for amino acid decarboxylase (AADC) to the putamen in patients with medically refractory Parkinson's disease (NCT01973543). This is the first use of MR-guided infusions in a gene therapy trial for a neurodegenerative disorder; a parallel study using the same technique is also enrolling patients at the NIH using AAV2 to deliver a gene encoding glial cell line-derived neurotrophic factor or GDNF (NCT01621581). Both of these trials utilize bilaterally mounted SmartFrames to allow for simultaneous infusions in both hemispheres. Our trial at UCSF is also the first-gene therapy trial to use a variable volume of infusion based on the visualized coverage of the putamen on real-time imaging.

These studies have demonstrated a significant issue that has likely limited the success of prior gene therapy studies in Parkinson's disease using traditional stereotactic techniques with blind infusions. Animal studies over a decade ago showed that perivascular spaces in the basal ganglia can shunt the infusate away from the intended target site [14]. This phenomenon has been seen during putaminal infusions in our current MR-guided gene therapy trial, which has prompted us to vary the infusion rates and cannula depth in real-time during infusions to mitigate the degree of non-targeted delivery of vector. The spread of vector away from the intended target is variable, but can be quite extensive. This has significant implications for the success of these trials, as it is believed that adequate coverage of the putamen may have a dramatic impact on the clinical effect seen.

Five-year view

Ongoing developments and accumulating experience with the technique and technology of drug formulations, CED platforms, and iMRI systems will continue to make local therapeutic delivery into the brain more safe, accurate, efficient, and effective. The latest iteration in the step design of the SmartFlow infusion cannula includes a shorter step, with the goal of further minimizing reflux, as well as a variety of step lengths to allow the surgeon to select the optimal catheter geometry for the target being infused. Implantation of multiple catheters for simultaneous infusions can be employed to cover larger targets with irregular shapes with greater efficiency. For example, bilateral simultaneous infusions are

currently being used for gene therapy trials for PD. Early experience with the system has illustrated the challenge in providing full coverage of targets using the infusions. In the cases of tumors, due to each lesion being unique in its shape and size, a custom volume of infusion is likely appropriate for full coverage of the tumor. We are continuing to gain experience with infusion of larger volumes at higher rates, with the goal of the infused agents being able to cover larger target lesions. In addition, an entirely implantable system including an implantable indwelling reservoir attached to an infusion cannula is currently being developed to allow for continuous, long-term infusions. With advances in planning software and accumulating experience with iMRI, prediction and modeling of infusion patterns will continue to be refined. For local therapeutic delivery to the brain, iMRI has proved to be an invaluable tool, providing unprecedented data on infusion physics that are key in guiding the ongoing evolution of delivery technology and techniques.

References

Papers of special note have been highlighted as:

- of considerable interest

1. Kunwar S, Prados MD, Chang SM, et al. Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol.* 2007; 25(7):837–844. DOI: 10.1200/JCO.2006.08.1117 [PubMed: 17327604]
2. Kunwar S, Chang S, Westphal M, et al. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. *Neuro Oncol.* 2010; 12(8):871–881. This summarizes the results of the PRECISE trial. DOI: 10.1093/neuonc/nop054 [PubMed: 20511192]
3. Sampson JH, Archer G, Pedain C, et al. Poor drug distribution as a possible explanation for the results of the PRECISE trial. *J Neurosurg.* 2010; 113(2):301–309. This reference highlights some of the challenges in clinical application of CED, and highlights the need for the ability to visualize infusions. DOI: 10.3171/2009.11.JNS091052 [PubMed: 20020841]
4. Mueller S, Polley MY, Lee B, et al. Effect of imaging and catheter characteristics on clinical outcome for patients in the PRECISE study. *J Neurooncol.* 2011; 101(2):267–277. DOI: 10.1007/s11060-010-0255-0 [PubMed: 20563833]
5. Christine CW, Starr PA, Larson PS, et al. Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. *Neurology.* 2009; 73(20):1662–1669. DOI: 10.1212/WNL.0b013e3181c29356 [PubMed: 19828868]
6. Eberling JL, Jagust WJ, Christine CW, et al. Results from a phase I safety trial of hAADC gene therapy for Parkinson disease. *Neurology.* 2008; 70(21):1980–1983. DOI: 10.1212/01.wnl.0000312381.29287.ff [PubMed: 18401019]
7. Muramatsu S, Fujimoto K, Kato S, et al. A phase I study of aromatic L-amino acid decarboxylase gene therapy for Parkinson's disease. *Mol Ther.* 2010; 18(9):1731–1735. DOI: 10.1038/mt.2010.135
8. Warren Olanow C, Bartus RT, Baumann TL, et al. Gene delivery of neurturin to putamen and substantia nigra in Parkinson disease: a double-blind, randomized, controlled trial. *Ann Neurol.* 2015; 78(2):248–257. DOI: 10.1002/ana.24436 [PubMed: 26061140]
9. Yin D, Forsayeth J, Bankiewicz KS. Optimized cannula design and placement for convection-enhanced delivery in rat striatum. *J Neurosci Methods.* 2010; 187(1):46–51. DOI: 10.1016/j.jneumeth.2009.12.008 [PubMed: 20026357]
10. Larson PS, Starr PA, Bates G, et al. An optimized system for interventional magnetic resonance imaging-guided stereotactic surgery: preliminary evaluation of targeting accuracy. *Neurosurgery.* 2012; 70(1 Suppl Operative):95–103. discussion. DOI: 10.1227/NEU.0b013e31822f4a91 [PubMed: 21796000]

11. Richardson RM, Kells AP, Martin AJ, et al. Novel platform for MRI-guided convection-enhanced delivery of therapeutics: preclinical validation in nonhuman primate brain. *Stereotact Funct Neurosurg.* 2011; 89(3):141–151. DOI: 10.1159/000323544 [PubMed: 21494065]
12. Krauze MT, Saito R, Noble C, et al. Reflux-free cannula for convection-enhanced high-speed delivery of therapeutic agents. *J Neurosurg.* 2005; 103(5):923–929. DOI: 10.3171/jns.2005.103.5.0923 [PubMed: 16304999]
13. Noble CO, Krauze MT, Drummond DC, et al. Novel nanoliposomal CPT-11 infused by convection-enhanced delivery in intracranial tumors: pharmacology and efficacy. *Cancer Res.* 2006; 66(5): 2801–2806. DOI: 10.1158/0008-5472.CAN-05-3535 [PubMed: 16510602]
14. Krauze MT, Saito R, Noble C, et al. Effects of the perivascular space on convection-enhanced delivery of liposomes in primate putamen. *Exp Neurol.* 2005; 196(1):104–111. DOI: 10.1016/j.expneurol.2005.07.009 [PubMed: 16109410]

Key issues

- Local delivery of therapeutic agents to the brain bypasses the blood brain barrier and minimizes systemic toxicity. Convection enhanced delivery (CED) utilizes continuous pressure gradient to distribute macromolecules into the interstitial spaces of the brain parenchyma across large volumes.
- Advancements in CED have included improved imaging and planning/ targeting platforms, allowing for better targeting, more accurate catheter placement, improved drug distribution.
- Previous challenge in clinical application of CED for central nervous system disorders has been the inability to visualize and confirm delivery of agents to the target sites.
- Applying interventional MRI for CED allows real time visualization of infusions, by using co-infusion of gadolinium. Advantages of real time CED include the ability to adjust cannula position or guiding placement of additional catheters to ensure optimal delivery and coverage of target sites.
- Real time CED is currently under active investigation in clinical trials for neuro-oncologic and neurodegenerative disorders. Early experience demonstrated successful infusions of neurotrophic growth factors, viral vectors and chemotherapeutic agents.

Figure 1. Patient positioning

The patient's head is fixed in an MRI compatible Mayfield fixation device attached to the MRI table. The prone position is also possible with elevation of the head off of the bottom of the bore.

Figure 2. SmartGrid for localizing the entry point

The localizing adhesive grid (SmartGrid) is placed over the approximate region of the preplanned entry site. The ClearPoint software generates an entry point within the SmartGrid for the entry site. Image courtesy of MRI Interventions.

Figure 3. Skull mounted SmartFrame

The SmartFrame houses a gadolinium impregnated fluid stem within the infusion cannula guide. This allows the software to automatically detect the trajectory of the cannula.

Figure 4. SmartFrame adjustments made in the 4 axes for target trajectory

Detecting the fluid stem allows the software to guide the alignment of the cannula guide to the target trajectory via adjustments made on the X–Y translational and the pitch-roll axes by knobs built into the frame. These adjustments can also be made using hand controllers extending out to the opening of the MRI bore for easy access to the neurosurgeon. Image courtesy of MRI Interventions.

Figure 5. Scalp mounted SmartFrame

This frame is able to mount directly onto the scalp through screws that puncture the scalp and secure onto the skull. At the entry point of the cannula, only a stab incision is made through the scalp, and a hand twist drill is used along the chosen trajectory to create a burr hole.

Figure 6. The infusion cannula connected to a MRI compatible pump
The catheter is connected to a syringe mounted on a MRI compatible infusion pump away from the sterile field.

Figure 7. SmartFlow cannula advanced and positioned for infusion

For the depth, the software generates the distance from the top of the guide stem (orange shaft) to the target, and a depth stop (black ring with red roll screw) is secured at this exact distance along the catheter (off white). After visualizing the fluid flow from the cannula tip, the cannula is then advanced through the guide tube into the brain to the target depth. Then the locking screw (clear with white roll screw) on the guide stem locks the infusion catheter at the target depth and the infusion is started.

Figure 8. Real time visualization of infusion

T1 MR images obtained during infusion demonstrates the co-infused gadoteridol that can be seen at the tip of the catheter. The gadolinium impregnated fluid stem and tip in the guide tube can also be detected to guide trajectory planning.