Methods of stereotactic drug delivery

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Drug delivery to the central nervous system (CNS) presents a significant challenge to researchers and clinicians due to the bloodbrain barrier. This is especially true for the delivery of small molecules, chemotherapeutics, nanoparticles, gene therapy and viral vectors, where in some cases toxic systemic levels of a drug may prevent a therapeutic level from being achieved in the CNS. Significant work is being conducted on bloodbrain barrier modulation and transient disruption to allow drugs in systemic circulation to more effectively permeate into the CNS. Alternatively, stereotacticbased methods are commonly employed in clinical practice to direct an infusion cannula to a desired anatomical location to provide for localized drug infusions and/or tissue biopsy.

Stereotactic methods have been intimately connected with the development of the neurosurgical armamentarium over the previous century. In modern practice, an apparatus or fiducial system is employed to match brain tissue and a prospective target to an imagebased coordinate system in threedimensional space. Before the introduction of stereotactic neurosurgery, direct visualization of the brain tissue via open technique was the only viable approach, and as such small or deep targets were often missed or difficult to locate. Moreover, transgression of eloquent brain tissue or critical vasculature complicated surgical intervention for deep targets. Because standard stereotaxy involves passage of a small cannula or needle into the brain, such as with deep brain stimulation, drug infusions, ablative techniques, or biopsies, morbidity is often reduced compared to a standard open approach.

Stereotactic techniques depend on a Cartesian coordinate system. Descartes observed the possibility to define a point in space using three orthogonal intersecting planes – commonly known as the X, Y, and Zplanes. Horsley and Clarke first described their stereotactic apparatus in 1908, and studied the cerebellum via lesions made at specific locations. Their contribution led to the development of a stereotactic brain atlas and apparatus for targeting electrolytic lesions.

Further refinements of the stereotactic apparatus were made over the ensuing years. As early as 1918, Mussen developed an apparatus for humans, though it is unclear if it was ever used. Adaptation of the animal apparatus for human use was difficult, primarily due to variability between landmarks on the skull and brain anatomy in and requirement for accurate placement in humans to avoid complications. In 1947, Spiegel and Wycis reported a new system to apply stereotaxy to humans that utilized internal landmarks from pneumoencephalography films. This system underwent multiple iterations until the Leksell arc system apparatus was developed in 1949, which propelled the modern field of radiosurgery in parallel. These techniques all required radiography to delineate internal landmarks, including pneumoencephalography or ventriculography. Modern imaging techniques, such as CT and MRI, provide more accurate targeting of intracranial lesions, such that accuracy is often determined by the quality and resolution of available imaging modalities.

Error in stereotactic methods

The historical gold standard for stereotactic procedures utilizes a framebased approach, however the use of frameless methods has also gained traction.

Frameless methods may be utilized irrespective of patient head size, neck configuration, and placement issues within an intraoperative MRI; however, frameless methods still rely on image guidance to a target despite no rigid immobilization. They utilize fiducial markers or skin or surface landmarks to correlate threedimensional operating room space to an imaging study. Numerous studies of framebased and frameless techniques have been conducted, and in general, framebased stereotaxy has a higher accuracy and precision for small, deep brain targets.

Precision and accuracy hinge on minimizing error during each step of a stereotactic procedure. Frame/fiducial application, image acquisition and manipulation, referencing to the fiducial system, surgical planning of the trajectory and target, patient positioning, and the surgical procedure itself all play a role in determining error. Moreover, a wellrecognized phenomenon in the neurosurgical literature is “ brain shift,” whereby the brain “ settles” or may move in response to gravity – which is most pronounced when CSF is lost and pneumocephalus occurs – or deforms in response to passage of a needle, lead, or cannula.

Intraoperative or postoperative imaging may be used to audit stereotactic targeting to compare actual target coordinates to those used initially for surgical planning. Finecut CT or MRI sequences may be conducted depending on hardware or frame compatibility. Stereotactic fluoroscopy may also be utilized to determine whether a target is placed appropriately.

In all, error in stereotactic neurosurgery is thought to be exceedingly small in most cases, which is essential in reducing clinical complications. The rate of

serious complications from framebased stereotactic procedures was reviewed in over 2, 600 patients: routine postprocedural imaging detected new blood products after a diagnostic biopsy in 2. 6% of cases (only 0. 4% required craniotomy for hematoma evacuation), periprocedural seizures occurred in 0. 4% of patients, and 0. 1% developed biopsy site infections.

Clinical Stereotactic Delivery Methods

While stereotactic methods may be used to bypass the bloodbrain barrier and deliver molecules to an intraparenchymal target, their penetration deeper into brain tissue may be limited by factors such as tissue permeability, diffusional coefficients, back pressure, and/or uptake and clearance mechanisms. As such, stereotactic methods are used to merely deposit a therapeutic agent, sometimes without the ability to control movement through the brain parenchyma itself.

ConvectionEnhanced Delivery

Pressuredriven infusion of molecules was first described in 1994 to introduce locally high concentrations of macromolecules and small molecules into the brains of cats using stereotaxy. The authors termed the pressuredriven infusion of molecules “ convectionenhanced delivery (CED),” as the distribution volume observed was greater than could occur by diffusion alone in the same time frame. CED utilizes a bulk flow formed by a hydrostatic pressure differential during infusion.

In CED, a stereotacticbased infusion cannula is directed to a target with controlled application of a positive pressure gradient to distribute the infusate within the brain parenchyma. The balance between infusion

parameters and tissue properties and the aforementioned tissue drag forces result in penetration for a molecule of interest. Perhaps the most attractive attribute of CED is its ability to directly bypass the bloodbrain barrier to achieve locallyhigh concentrations of a therapeutic agent at a given target. In the simplest theoretical model, convective velocity emanates from a central cannula source in a spherical manner in accordance with Darcy’s law. [26] In practicum, predicting the infusion profile is more difficult, though several theoretical models have been postulated to account for tissue binding, metabolism, and porosity of the tissue itself.

As the CED methodology was explored over the nearly two decades to the present date, the rates of infusion, infusion cannula size, concentrations of the infusate, and preinfusion sealing times to allow accommodation of the infusion cannula were systematically studied. More than 17 human clinical trials and numerous animal studies have examined the effectiveness and safety profile of CED. Despite clear efficacy in delivering localized infusates into the central nervous system, pressuredriven CED remains limited by backflow of the infusate along the implanted cannula tracts, especially at moderate to high flow rates, mass effect and edema (with or without focal neurological deficit or seizure) from large infusion volumes, and difficulty with infusion cannula placement and the directional control of infusate once inside the brain. Moreover, deep tissue deformation, separation and tearing of white matter tracts, leakage of the infusate into the cerebrospinal fluid spaces and/or prior surgical resection beds, and seepage along vascular or cannula tracts, have all been documented to contribute to sometimes unpredictable intraparenchymal drug delivery.

CED remains an important strategy for the delivery of molecules and agents to deep targets within the brain despite clear limitations. As an example, a Phase 1B clinical study recently completed enrollment, whereby CED was used to infuse a gene promoting aromatic Lamino acid decarboxylase expression (the enzyme converting levodopa to dopamine) via an adenoassociated viral vector to the putamen of human patients with Parkinson’s disease (Voyager Therapeutics).

Focused Ultrasound Therapy

The first work to describe potential applications of high intensity focused ultrasound was in 1942 and built upon over the subsequent decade when Fry et al. produced lesions in the brains of cats and monkeys. Research into the use of this technique continued through the 1950’s and 1960’s, but technical limitations restricted their adoption in clinical practice. Initial efforts using focused ultrasound aimed to created lesions in tissue for functional outcomes or in malignancies.

High intensity focused ultrasound causes tissue damage via two primary mechanisms: the conversion of mechanical energy to thermal energy and cavitation. If the rate of heating exceeds the rate of cooling in brain tissue, the net effect is a local temperature rise. Sustained temperatures above 43 degrees Celsius for more than 60 minutes are thought to cause arrest of cellular activity. High intensity focused ultrasound rapidly causes local temperatures of more than 56 degrees Celsius with coagulative necrosis ensuing after only a few seconds to minutes. In contrast, cavitation is complex and difficult to predict. The tissues vibrate and gas can be drawn from solution to form bubbles, which oscillate in size or collapse rapidly. This

forms mechanical stresses to a local region of tissue and high local temperatures. Cavitation is dependent on pulse length, frequency, and intensity. High intensity focused ultrasound has been used in the treatment of CNS tumors (benign or malignant) or in functional neurosurgery to create lesions, such as thalamotomies for tremor or chronic pain.

In contrast, newer focused ultrasound techniques also aim to disrupt the bloodbrain barrier to aid therapeutic drug delivery, rather than simply creating lesions in the CNS. These applications typically utilize low intensity focused ultrasound, in contrast, to transiently disrupt the bloodbrain barrier with preformed microbubbles. Typically performed with use of an intraoperative MRI, focused ultrasound therapy may be performed in a transcranial fashion. Issues relating to the skull have been addressed as well, including heating of the skull and inaccurate beam propagation due to heterogeneities (such as bone shape, thickness, marrow density, etc). MR thermometry is further utilized to guide focused low intensity ultrasound treatments in real time, such that temperatures on the range of 4042 degrees Celsius were possible without permanent damage or lesioning. No largescale human clinical trials regarding bloodbrain barrier disruption have been completed as of present date, despite enormous preclinical and experimental promise.