Advances in Neurotherapeutic Delivery Technologies

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Convection-Enhanced Delivery of Neurotherapeutics

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Abstract

Study background: The delivery of therapeutic drugs to the brain is a challenging task despite the fact that brain is highly accessible for other substances like nutrients and oxygen. Effective targeting of drugs to the CNS is essential for future success of neurotherapeutics; however the delivery of potentially effective neurotherapeutics to specific areas of the brain is restricted by Blood-Brain-Barrier (BBB). Convection-Enhanced Delivery (CED) has proven to overcome this challenge.

Methods: ICED is a method that employs a fluid pressure gradient established at the tip of an infusion catheter and bulk flow to propagate substances within the extracellular fluid space. This allows for safe, targeted, reliable homogeneous delivery of small and large molecular weight substances in a manner that bypasses the BBB. This Chapter seeks to provide a detailed overview of several CED methods that have been used to enhance the delivery of drugs to the brain for the treatment of various neurological diseases, assessing most the success, problem areas and the future strategies for using CED.

The discussion of these methods ranges from among others
i) Employment of catheters for CED;
ii) Computer-aided drug distribution in CED;
iii) Image-guided CED;
iv) Laser energy-aided CED and
v) Time-reversal techniques in ultrasound-assisted CED.

The Chapter also aims at providing a subtle insight into the application of convection-enhanced drug delivery in neurotherapy.

Results: CED has shown the capacity to safely bypass the BBB and deliver therapeutic
agents of varying sizes to specific targets within CNS. CED results into homogeneous distribution of drug solutes that can perfuse clinically relevant volumes of the CNS at effective therapeutic concentrations. Either, the development and use of surrogate imaging agents have made it possible to track the convective delivery via real-time imaging

**Conclusion:** The achievements so far obtained with CED, hold a great promise in the treatment of a variety of intrinsic neurological brain disorders in the future.

**Keywords:** Blood-Brain-Barrier (BBB); Brain tumor; Catheter; Central Nervous System (CNS); Convection-Enhanced Delivery (CED); Drug Delivery; Imaging; Infusate; Neurotherapeutics; Real-Time MRI

**Introduction**

Effective drug delivery to the brain has remained to be the greatest challenge in the treatment of many Central Nervous System (CNS) disorders. Despite the fact that there has been a great advancement in the development of potent neurotherapeutic agents in vitro, their application and efficacy in vivo meets a formidable challenge due to the limitations associated with currently available delivery techniques. Existing CNS delivery techniques are:

i) Systemic delivery;

ii) Intrathecal or Intraventricular administration and

iii) Polymer implantation [1,2].

Apparently, systemic delivery is restricted by systemic toxicity, non-targeted drug distribution and the failure for the majority of therapeutic agents to cross the Blood Brain Barrier (BBB). Furthermore, brain structural components, are said to have varying interstitial pressures which also contribute to the limitations found with systemic delivery [3]. Intrathecal or intraventricular administration as well as polymer implantation are both diffusion-dependent methods that are limited by non-targeted distribution, inhomogeneous dispersion and ineffective volume of distribution. To date, a lot of research studies have been done to investigate the potential for Convection Enhanced Delivery (CED) to deliver therapeutics agents into the nervous system [4-6] in the attempt to overcome the problems associated with the currently available delivery methods. What has been observed from the results of these studies is that direct perfusion of CNS interstitial spaces using convective distribution allows for safe, reliable, targeted, homogeneous delivery of therapeutic agents (low and high molecular weight compounds), into small and large brain tissues, at clinically relevant volumes in a manner that bypasses the BBB [2,3,7]. Furthermore, these studies have shown that the convective co-infusion of a mixture of therapeutic agent and an imaging surrogate tracer can now be used to monitor drug distribution in real time using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) [8]. These unique features of CED allow for the development of new drug delivery paradigms for the treatment of various central nervous system disorders.

CED is a highly technical process involving stereotactic placement of one or more catheters through cranial burr holes directly into brain tumors or tissue. A therapeutic agent is normally administered continuously through the catheters employing a microinfusion delivery system to create a positive pressure gradient at the catheter tip. As the pressure builds up, it creates fluid convection flow to augment the diffusion process through the extracellular spaces thereby enhancing the distribution of the drug to the targeted area. Figure 1a is schematic model depicting convection-enhanced delivery. The principle of operation for the CED technique is that there is a bulk flow of the infusate that becomes
driven by a small hydrostatic pressure that is normally obtained by maintaining pressure at the catheter tip using a syringe pump (Figure 1b) [9]. By the use of a micro-infusion pump, molecules are infused through a cannula that has been inserted into the target site. Continuous positive pressure, driven by the micro-infusion pump (black arrow in Figure 1b) becomes maintained at the tip of the cannula leading to the development of a pressure gradient. It is this pressure gradient that ultimately provides the convective flow or bulk flow that pushes the molecules away from the cannula tip (Figure 1b).

![Figure 1: a) A schematic model depicting convection-enhanced delivery with catheters placed into the enhancing tumor to cover the region of effect; b) principle of convection-enhanced delivery using a micro-infusion pump [9].](image-url)

What CED seeks to achieve is to:

i) Provide homogenous distribution of a therapeutic agent to a larger volume of brain tissue;

ii) Provide higher drug concentrations directly to the tissue and

iii) Be able to make use of molecules that cannot cross the Blood Brain Barrier (BBB).

BBB is formed of tight junctions between endothelial cells that make up the capillaries in the brain. Principally, it blocks polar and high molecular weight molecules from entering the parenchyma of the brain. Direct intraparenchymal brain infusion via CED has shown to overcome the limitations of previous therapeutic drug delivery methods and allows the use of therapeutic agents which previously failed to cross the BBB and therefore considered to be a non-viable treatment option [9]. CED has been proposed as a treatment option for a broad spectrum neurological disorders including malignant brain tumors [9-16], epilepsy, metabolic disorders, neurodegenerative diseases (such as Parkinson disease) [17], stroke and trauma [18]. Notably, the CED method has been employed in delivering a variety of therapeutic agents both in preclinical and early clinical studies aimed at combating neurodegenerative diseases such as Progressive Multifocal Leukoencephalopathy (PML) and Gaucher's disease [19].

**Attributes of convection-enhanced delivery with regards to safety and reliability**

During convective distribution of infusate within the interstitial spaces of CNS, the generated hydrostatic pressure gradient permits the movement of solute through extracellular spaces at bulk volume and speed that is several orders of magnitude greater than those associated with simple diffusion. The rate of infusion for convective delivery typically ranges from 0.5 to 6mL/min. Bulk flow properties is one of the unique features of CED. The distribution of infusate occurs in the interstitial space that allows the volume of distribution...
associated with convection to be substantially larger than the volume of infusion. As such the volume of distribution is inversely proportional to the interstitial fraction of tissue. Due to the fact that CED gives the provision for the attainment of large ratio of volume of distribution/volume of infusion as schematically illustrated in Figure 2, a relatively small volume of infusion can be distributed over a clinically relevant volume of distribution. Furthermore, since CED relies on bulk flow for infusate distribution instead of diffusion, a significantly larger volume of homogeneous distribution can be achieved with convection than with simple diffusion-driven methods such as intrathecal or intraventricular delivery or polymer implantation. Thus, infusate diffusivity is predominant in CED techniques since large Volume of distribution (Vd) can be achieved compared to those obtained after a classic diffusion method. This is schematically elaborated in Figure 3. Preclinical studies using radiolabeled infusate have consistently demonstrated that the concentration of infusate is similar over the entire perfused region [8,14,20]. Studies previously conducted by Lonser and Chen [21] have demonstrated that large regions of CNS (i.e. holohemispheric, brainstem and multiple vertebral levels of the spinal cord) and peripheral nervous system can be successfully perfused using CED. With regards to safety, Lonser and co-workers [21,22] demonstrated through animal and clinical studies that large volumes within CNS can be safely perfused using CED [21,22]. Their histopathological studies following a convective delivery of therapeutic agents revealed only mild gliosis with the use of infusion cannula tract within a 50m radius [23].

![Figure 2](image)

*Figure 2: A schematic depicting stereotactic injection in rat brain by: (A) classic diffusion method; versus (B) convection-enhanced delivery [24].*

Essentially in CED, diffusion and convection take place simultaneously as depicted in Figure 3. Diffusion is entirely dependent on the concentration gradient on one hand and on the diffusivity of the infusate in a specific tissue on the other hand. Diffusion occurs throughout but is essentially dependent on the nature of the infusate. Via CED, the therapeutic agent is mainly distributed within the interstitial spaces of the tissue by convection process with bulk flow which is strictly dependent on the pressure gradient, that occurs throughout the establishment of the pressure gradient.

**The fundamental technique for convection-enhanced delivery**

Implanting one or more catheters into the brain followed by the connection of an infusion pump to the catheter and then pumping the therapeutic agents through the catheter directly into the targeted region was the first method to be employed in CED [25]. The increased distribution fraction and relatively stable concentration was said to occur as the positive pressure created by the infusion pump caused the tissues to dilate and allow for permeation
of the drug [26]. To date, the fundamental technique for CED has principally remained to be the same i.e. as the first one. However, there have been some advances to increase the safety and efficacy of treatment [26]. These advances are in catheter design [26], infusion technique [27], line pressure monitoring and real time MRI monitoring to correct for brain shift [28,29], optimize multiple collinear infusions [30] and monitor for infusate loss [31]. Additional importance has been placed on the catheter design and infusion strategy including the flow rate.

Figure 3: Schematic representation of CED mechanism: A) identification of the target site with correct placement of the catheter according to specific coordinates; B) diffusion which occurs all the time but is rigorously dependent of the infusate nature and C) convection (or bulk flow) which is strictly dependent on the pressure gradient and occurs during all the establishment of the pressure gradient [24].

The most successful CED methods are those with limited catheter reflux and tissue damage properties that are correlated to catheter design and infusion rate. It has been shown that catheters with a narrow diameter and a low infusion rate can limit backflow along the brain-catheter interface as well as damage at the catheter tip [31]. Fiandaca and co-workers [32] have shown that MR imaging provides visual confirmation of the correct location for infusion catheter placement, and thus drug delivery, while also allowing for correction of infusion reflux or anomalous delivery. It has also been revealed that MR images may be also be used to approximate and track the volumes of distribution (Vd) of the infused drug [33]. The Vd is calculated using an MR imaging signal intensity value greater than three standard deviations above the mean from the surrounding non-infused gel as a threshold for segmentation [33]. The Vd has been shown to be a useful measurement for CED since it represents the volume of the drug that has been distributed into the brain. By using the Volume infused (Vi), a ratio may be generated (Vd/Vi) that quantifies the volume covered by the infused drug.

This Chapter therefore seeks to provide a detailed overview of several CED methods that have been used specifically for neurotherapeutics delivery to the brain for the treatment of various neurological diseases, assessing most the success, problem areas and the future strategies for using CED.

The discussion of these methods ranges from among others;

i) Employment of catheters for CED;

ii) Computer-aided drug distribution in convection-enhanced delivery of neurotherapeutics;
iii) Image-guided CED;
iv) Laser energy-aided CED and
v) Time-reversal techniques in ultrasound-assisted convection-enhanced drug delivery to the brain.

The Chapter also aims at providing a subtle insight into the application of convection-enhanced drug delivery in neurotherapy.

**Convection-Enhanced Methods Involved in the Delivery of Neurotherapeutics**

**Employment of catheters for convection-enhanced delivery of drugs**

**Reflux-preventing Catheters**

The first infusion tool to be employed in CED was a needle that was implanted into the CNS of experimental animals [34] but later on, it appeared to be logical to use a more practical and flexible method for clinical application which was to use a catheter in CED instead of a needle. A catheter was more advantaged in the sense that it could be stereotactically placed in CNS and delivers the infusates through a port at the distal end (Figure 4) [9]. Employed more frequently in clinical trials are the barium-impregnated Medtronic® PS Medical catheters (Goleta, CA, USA; Catalog number 43209) and Vygon US LLC (Valley Forge, PA, USA) which are all one port catheters [35]. Fiandaca and co-workers [32] later observed that extension of the end of the tip of a lead catheter with a smaller gauge catheter facilitates the prevention of infusate reflux, an undesirable event that may render the CED process unsuccessful. Fiandaca and co-workers [32] therefore managed to construct a step design cannula that allows CED at flow rates as high as 5.0µL/min without any reflux tendencies (Figure 4).

**Hollow fiber and multi-tipped catheters**

Porous hollow fiber catheters were catheters developed with an intention of increasing the surface area of that part of the brain that has a direct contact to the released drug i.e. the volume of tissue exposed to the delivered drug (Figure 4) [36]. A hollow fiber is endowed with millions of nano-openings (0.45µm) along its wall. It has been observed that a hollow fiber can offer up to a three-fold increase in the volume of distribution (i.e. of the drug) into normal mouse brain when compared to a needle-mediated infusion [36]. It has also been established that in order to obtain a desirable success with CED methods, catheters with multiple openings ought to be used [25]. However, the practice has shown that efficient release of the infusate via these types of catheters may only happen through the proximal port therefore making no difference from a one-port catheter in terms of performance (Figure 4) [25].

**Balloon-tipped catheter**

A balloon-tipped catheter (Figure 4) is another type of catheters which has been designed to augment the efficiency of CED for the management of the cancer of the brain. As opposed to standard one-port-at-the-tip catheters, this catheter has a balloon just before the catheter tip which may be inflated to fill a resection cavity that culminates into limiting the tendency for reflux to occur thereby pushing the infusate into the tumor parenchyma [9]. Olson and co-workers [37] studied this catheter in normal canine CNS by comparing it with a similar balloon catheter that was devoid of a distal opening. The later catheter was made to deliver brachytherapy through GliaSite radiation therapy system [37] using organically bound
125Iodine radiotherapy solution in recurrent glioma that required resection. The study outcomes demonstrated that the inflated balloon resulted into an extensive/continuous delivery of the infusate to the canine model [37]. These results were considered to be very successful thus leading to a proposal for employing both the balloon-tipped catheters and multiple catheters around the resection cavity during CED-based type of therapy.

Computer-aided drug distribution in convection-enhanced delivery of neurotherapeutics

Prediction of the individualized CED-based drug distribution employing computer software

Like in any invasive procedure, it is considered to be most appropriate to plan CED basing on standardized parameters customized to suit an individual patient. BrainLAB AG company (Feldkirchen, Germany) is one the companies that have successfully developed a commercially available US FDA-approved software. This software utilizes data input obtained by MRI with regards to brain tissue characteristics of an individual patient. The calculations involved are mainly targeted at obtaining desired drug distribution volume in which case, the plan for treatment may be visualized in 3D, including the number and position of catheters [39]. The software has been clinically examined in a retrospective manner using the data obtained from magnetic resonance diffusion tensor imaging. Taking into account the individual characteristics of a patient’s anatomy and pathophysiology for the initial plan of CED, the software has been found to be potentially useful in addition to the existing personalized surgical management.

Computer modeling of convection-enhanced drug delivery to the brain

It is now well known that treatment of neurological disease has been impeded by the limited drug diffusion across the BBB. Much as CED method has been proven to circumvent the BBB, the bottle-neck fact is that transport of a drug in a patient’s brain following CED is often difficult to predict due to the brain’s anisotropic properties, which differ according to direction of measurement. It has been shown that computer-assisted modeling and simulations can serve as powerful tools for predicting the drug distribution in
a patient’s brain before delivering the drug [40]. To reconstruct the patient’s brain geometry accurately using medical imaging data and software, followed by the application of rigorous mathematical equations to these models may provide physicians with information about the brain’s mechanism and pathology. Such medical imaging techniques like MRI and computer tomography (CT) can provide qualitative images of a patient’s brain, but they can’t provide quantitative measure of transport in the brain due to diffusion and convection.

Computer aided simulations may serve as virtual therapy for surgeons before they conduct clinical trials using convection-enhanced delivery. They have shown to be able to predict the pressure and velocity of the drug in an individual patient’s brain and model state changes of drug delivery that cannot be obtained experimentally [41]. The results of the simulation can be compared to experimental data and imaging to evaluate the accuracy of the simulation. If the simulations match the experimental data, then it can be concluded that the remainder of the simulation results will resemble drug transport in the patient’s brain once convection-enhanced delivery is administered. These results may be used to design patient-specific treatments and make decisions regarding catheters and stents for drug delivery in an attempt to achieve a particular local concentration or steady-state concentration.

ANSYS is one of the software’s used to reconstruct patient’s brain geometry and obtain drug velocity and pressure in the brain following convection-enhanced delivery. These computer-simulated models can provide data that cannot be easily obtained from experimental tests. The software employs equations similar to the ones used in computational fluid dynamics analysis and contains a plethora of processing features that allow results to be easily viewed and interpreted. ANSYS software has a great potential for designing patient-specific drug administration using CED.

**Image-guided convection-enhanced delivery**

**Real time imaging of drug distribution**

It has been observed that the volume of distribution and the anatomic distribution of the infusate varies with the site of treatment [42]. Furthermore, the distribution of the infusate in the extracellular space of the brain has been shown to be influenced by tissue heterogeneity [42]. Thus, to obtain the desired output and optimal clinical use of convective delivery, direct visualization of the distribution of the infused agent in the CNS during infusion, is an important undertaking. Thus far, small and large molecular weight CT and MRI tracers that can be co-infused with therapeutic compounds during CED have been developed and investigated [42]. It has been observed that mixing therapeutic agents and imaging surrogate tracers or encapsulating drugs in labeled liposomes, gives the provision for the precise monitoring of small or large molecule distribution in real time using serial CT or MRI [43]. The ability to monitor the distribution of infusate in a noninvasive manner in real time, improves the accuracy of infusion, ensures adequate target perfusion, and gives provision for the accurate determination of the efficacies of various therapeutic agents.

**Magnetic resonance imaging-guided convection-enhanced delivery**

**Assessment of cytotoxic tissue response by subsequent diffusion-weighted magnetic resonance imaging**

MRI that was acquired immediately post-treatment with infusates mixed with Gd-DTPA. It was shown that poor convection was a result of significant backflow along the catheter and into the ventricles [45]. Significant spread of the infusate into the striatum with minimal
backflow into the ventricles was a clear sign of efficient convection. Figure 5 portrays the examples of poor, moderate and good convections.

**Laser energy-aided convection-enhanced delivery**

**Laser energy-mediated convection-enhanced simultaneous co-delivery of fluids with a fiberoptic microneedle device**

Recent advancement in neurotherapeutics delivery, have resulted into the development of new and model CED techniques for which an infusion catheter which makes use of a Fiberoptic Microneedle Device (FMD) is one among others. FMD is a device that employs photo energy for enhancing the dispersion of the infused neurotherapeutic agent to the brain tumor [47]. Principally this technique utilizes laser energy-derived type of delivery whereby the laser energy causes mild localized photothermal heating (4-5°C) that ultimately leads to an increase in the dispersibility of the infused neurotherapeutic agent [47]. Further development of FMDs coupled with laser energy-mediated photothermal CED may provide room for a greater distribution of neurotherapeutics during CED therapy of brain tumors.

![Figure 5: A and B, T1- and T2-weighted axial MRI of normal rat brain. C, D and E, T1-weighted MRI acquired immediately post-CED treatment with infusates containing Gd-DTPA and Evans blue, showing examples of different convective efficiency as depicted by MRI: poor (C), moderate (D) and efficient (E) convection. F, G and H fixed brain samples of the same rats demonstrating similar distributions of the dye in the tissue [46].](image)

**Time-reversal techniques in ultrasound-assisted convection-enhanced drug delivery to the brain**

**Time Reversal Acoustics (TRA)**

Accurate focusing of ultrasonic waves is the most important aspect of most medical applications of ultrasound [48]. Quite often, the degree with which the ultrasound focusing of biological tissues can efficiently be carried out, is affected by spatial heterogeneities in sound velocity in tissues and also by the presence of reflective surfaces and boundaries [48]. Refraction, reflection and scattering of ultrasound in inhomogeneous media may easily
distort a focused ultrasound field. There are several methods that may be used to improve ultrasonic focusing in complex media but most of them are often too complicated. Time-Reversal Acoustics (TRA) concept has been found to be an alternative technique for focusing acoustic energy in inhomogeneous media which is as such simple and elegant [48]. TRA is a technique of focusing ultrasonic waves which is typically based on the reversibility of acoustic propagation, implying that the time-reversed version of an incident pressure field naturally refocuses on its source [49,50]. Figure 6 is schematic diagram comparing the difference between TRA and phased-array focusing.

A) Focused arrays require complex phase correction and image-guidance to account for aberrations of the acoustic field by the skull;
B) A simple reverberator placed on the outside of the skull whereby TRA principles may be used to focus energy with as little as one or two channels;
C) Currently one of the largest limitations of CED is the ability to control the infusion (red) to target the migrating cancer cells (yellow/red) and
D) TRA-UCED that may provide a minimally invasive approach to improve CED with transcranial delivery of ultrasound.

![Figure 6: Time-Reversal Acoustic (TRA) application for drug delivery in the brain [48].](image)

**Ultrasound-assisted in vivo technique for convection-enhanced delivery of therapeutic agents with a transducer cannula assembly**

It has been demonstrated that ultrasound Transducer Cannula Assembly (TCA) apparatus may be used for the delivery of therapeutic agents to several targets in the body including cells, tissues or an organ in a healthy or diseased state [50]. The ultrasound TCA apparatus comprises a Transducer Cannula Assembly (TCA) and an ultrasound system for enhancing the penetration of molecules into the target (Figure 7) and it may be portable and pocket-sized. Notably, the inclusion of ultrasound in the apparatus improves the distribution volume of material 4 to 6 times compared to a CED system without ultrasound. With this technique, targeting can be more focused thereby allowing the use of less therapeutic agent, thus lowering the potential for harmful effects to the host and host cells.
Ultrasound-assisted convection in brain tissue

It has been observed that much as it is possible to successfully employ CED to deliver therapeutics locally at concentrations that exceed systemic toxicity limits, the challenge lies in the difficulties with which compounds can be delivered to specific target sites [48]. Research has shown that for small molecules that become infused using CED, the average convective velocity may be fairly large but that of proteins and nanoparticles is considerably smaller because their transport is hindered by their pore sizes (approximately 100nm) [51]. Studies have shown that ultrasound in plane wave and focused applications can enhance convective transport of compounds through muscle and brain tissue \textit{ex vivo} [48,51-53] an effect that has been exploited \textit{in vivo} by Lewis and co-workers [48]. These researchers (i.e. Lewis and co-workers) managed to establish a research-based evidence that ultrasound can be combined with convection transport to increase the penetration of tracers in the rodent brain using some special designed transducers and cannulas. In this technique, ultrasound-assisted CED was employed by performing a small craniotomy on the rodent under anesthesia and then carrying out the infusion process with a micro pump at 0.25 to 1μL/min with simultaneous exposure to 1.34 MHz low intensity ultrasound for the entire duration of the infusion process as depicted in Figure 8. In this experiment relativity low acoustic intensities (47–150 mW/cm²) were observed to increase the (Vd) of Evans Blue Dye (EBD) by 1.16 to 3.25 times as compared to the control depending on exposure parameters including time, infusion rate and acoustic intensity/duration. Despite this success, the underlying mechanisms are still not very clear. However, acoustic streaming, mechanical wave interaction with the poroelastic matrix, increased tissue permeability, acoustic dispersion and intersitium swelling are all said to be the potential candidates contributing to the improved distribution.

The summary of technical parameters relevant to effective Convention-Enhanced Delivery (CED) and their impact on Volume of distribution(Vd) and backflow is provided in Table 1.
A plane wave transducer with cannula through-hole is mounted on top of the rodent brain through a small craniotomy window in the skull. Infusion at 0.5μL/min of EBD with and without continuous wave ultrasound operating at $I=47\text{mW/cm}^2$ for 30 minutes; (B) 3-dimensional reconstruction of infusion volume with (UCED) and without (CED) ultrasound exposure; (C and D) brain slices in the cannula path showing EBD distribution with (UCED) and without (CED) ultrasound exposure.

**Figure 8:** A schematic depicting an ultrasound-assisted Convection Enhanced Delivery (UCED) to the rodent brain [48].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Vd</th>
<th>Backflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter</td>
<td>High conductivity</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>Low conductivity</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Tumor tissue</td>
<td>Modified conductivity</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Bad insertion</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Distance to target</td>
<td>Large distance</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Distance to target</td>
<td>Short distance</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Large</td>
<td>&lt;28 gauge</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Small</td>
<td>≥32 gauge</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Infusion rate High</td>
<td>2-5μL/min (rodents)</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Low</td>
<td>≤0.5μL/min (rodents)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Reflux-free</td>
<td>Glued-in-fused silica tubing</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Multiple hole</td>
<td>Irregularly shaped Vd</td>
<td>+</td>
<td></td>
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<tr>
<td>Single end port</td>
<td>Spherical distribution</td>
<td>+++</td>
<td></td>
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<tr>
<td>Bone wax fixed</td>
<td>Increased pressure</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Primed cannula</td>
<td>To prevent air bubbles</td>
<td>+++</td>
<td></td>
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<tr>
<td>Infusion volume</td>
<td>Increased Vi</td>
<td>Linear relationship Vd/Vi</td>
<td>+++</td>
</tr>
</tbody>
</table>

Vd - Volume of distribution; Vi - Infusate volume

Vd and backflow are qualified as high (+++), moderate (++) and low (+).

**Table 1:** Summary of technical parameters relevant to effective Convention-Enhanced Delivery (CED) and their impact on Volume of distribution(Vd) and backflow [23].
Application of Convection-Enhanced Drug Delivery in Neurotherapy

Employment of convection-enhanced delivery in neuro-oncology

It has been observed that tumors originating from glial cells (referred to as gliomas) account for almost 80% of primary malignant brain tumors [24]. Astrocytomas is a heterogeneous group of tumors that range from low grade to the most aggressive, Glioblastoma Multiforme (GBM), based on histopathological classification (from grade I to IV) in accordance to World Health Organization (WHO). What makes GBM different from other types of cancers, is its high degree of diffuse invasion of the surrounding normal tissues as well as its high recurrence rate after all types of therapy.

Conventional therapy for brain tumors encompasses surgical biopsy for pathological diagnosis and essentially the first treatment is tumor resection, followed by fractioned external beam radiotherapy and systemic or oral chemotherapy [54-56]. It has been observed that despite all these sets of treatments, the prognosis for patients with glioblastoma has remained to be relatively poor over the last three decades [56-58]. CED has proven to be the breakthrough for the failure encountered by anticancer drugs to cross the BBB and therefore the most practical method for treating gliomas. CED enables the local delivery of a wide range of anticancer agents including conventional chemotherapeutic agents [59,60], monoclonal antibodies [61,62], targeted toxins [63,64], proteins [65], viruses [66] and nanocarriers [67-69]. For the effective functioning of CED, the activity of the anticancer agent has to be considered but most critical parameter is technical drug delivery approach. Obviously, a uniform distribution of an effective agent in tumors will ultimately influence the therapeutic efficacy and this is where the properties of each infusate come to importance. Nanocarriers (e.g. lipid nanoparticles, micelles, liposomes and dendrimers) are generally used to transport drugs that are often very sensitive, toxic, hydrophobic or for targeting a specific organ that happen to be cancerous [70].

Nanopolymers, lipid nanoparticles, micelles, liposomes and dendrimers as vehicles for convection-enhanced delivery

Generally nano-based vehicles have got several advantages including the ability to protect the active ingredient from \textit{in vivo} degradation and the reduction of toxic side effects which often leads to an increase in patient compliance. Due to the possibility of grafting specific ligands to their surface, nanocarriers can recognize specific targets [55] which is another advantage. Nanoparticles may also bypass Multidrug Resistance (MDR) mechanisms by inhibiting efflux pumps such as P-glycoprotein (P-gp), and optimizing the bioavailability of anticancer agents [71-73]. Thus far, liposomes, nanoparticles, dendrimers and polymeric micelles are some of the nanocarriers that have been employed in CED methods.

An ideal nanocarrier should have a high drug-loading capacity so as to be able to eradicate the tumor and should also be labelled with contrast agent in order to realize real-time imaging. Furthermore, ideal nanocarrier should have a size range of 20-50nm, with a global neutral or negative charge and shielded by for instance a steric coating made of PEG or dextrans (Figure 9A). The final infused suspension should be viscous, hyperosmolar with eventually the presence of co-infusate to saturate the binding sites along the nanocarrier route (Figure 9B). For the nanocarriers purposely made to target the intracellular compartment, the final infused suspension should have a high concentration. Most important for nanocarriers is that their elimination route has to be controlled in order to prevent a rapid elimination by blood capillaries in brain extracellular matrix (Figure 9C).
Gene/protein-based therapy employing convection enhanced delivery

**Rationale for the use of convection enhanced delivery for gene delivery**

CED is one of the strategies that have been found to have the capability of covering larger areas of the brain with neurotherapeutics [32]. The method uses programmable pumps and specifically designed injection catheters for delivering therapeutic agents like Adeno-Associated Virus type 2 (AAV-2) vector to the nonhuman primate striatum in an efficient and reproducible manner when compared to single injections of smaller volumes [74]. It has been proved that CED approach has the potential for achieving comprehensive delivery to the striatum/globus pallidus/subthalamic nuclei using AAV-2 vectors [74]. Furthermore, it has been shown that gene delivery may also be more appropriately imaged in real time using co-injections of liposomes containing gadolinium or gadolinium bound to albumin [75]. Figure 10 is a schematic depicting the translation of gene therapy to humans using CED. Further applications of CED in neurotherapeutics are summarized in Table 2 which displays the drugs/bioactives, disease conditions, and methods employed in Convention-Enhanced Delivery (CED).
**Figure 10:** A schematic portraying the translation of gene therapy to humans through convection enhanced delivery [17].

<table>
<thead>
<tr>
<th>Drugs/bioactives</th>
<th>Disease condition/s</th>
<th>Convection-enhanced delivery method/s employed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conotoxin N-type calcium channel antagonants (selective N-type calcium channel inhibitor)</td>
<td>Focal epilepsy</td>
<td>CED using a step-design cannula and a microfabricated probe with a side-positioned exit port type of catheter</td>
<td>[2]</td>
</tr>
<tr>
<td>Botulinum neurotoxins (inhibitors of neurotransmitter; specifically inhibit glutamate release)</td>
<td>Partial epilepsy</td>
<td>CED using a step-design cannula and a microfabricated probe with a side-positioned exit port type of catheter</td>
<td>[2]</td>
</tr>
<tr>
<td>Cintredekin Besudotox (CB)</td>
<td>Glioblastoma Multiforme (GBM)</td>
<td>Intracerebral CED using reflux-preventing catheters</td>
<td>[14]</td>
</tr>
<tr>
<td>siRNA, and viral vectors</td>
<td>Parkinson's disease</td>
<td>Low-flow neurocatheter infusion-based CED using the Alaris® infusion system</td>
<td>[20]</td>
</tr>
<tr>
<td>Adeno-associated virus 2 carrying human amino acid decarboxylase gene (AAV2-hAADC)</td>
<td>Parkinsonism</td>
<td>Time-reversal ultrasound-assisted CED using a step-design cannula</td>
<td>[32]</td>
</tr>
<tr>
<td>Glucocerebrosidase</td>
<td>Gaucher's disease</td>
<td>Real-Time MRI guided CED</td>
<td>[42]</td>
</tr>
<tr>
<td>Gliadel®</td>
<td>Glioblastoma Multiforme (GBM)</td>
<td>Time-reversal ultrasound-assisted CED using hydrophone infusion catheter</td>
<td>[53]</td>
</tr>
<tr>
<td>Cotara™ (I^{131}-labeled Chimeric Monoclonal Antibody)</td>
<td>Malignant solid tumors</td>
<td>CED using multiple port catheter</td>
<td>[64]</td>
</tr>
<tr>
<td>Interleukin-13 conjugated to cintredekin besudotox (PE38QQR)</td>
<td>Recurrent malignant gliomas</td>
<td>High flow micro-infusion-based CED using reflux-preventing catheters</td>
<td>[76]</td>
</tr>
<tr>
<td>Interleukin 13 bound to a Pseudomonas toxin (IL13-PE)</td>
<td>Diffuse brainstem gliomas</td>
<td>Real time imaging CED</td>
<td>[77]</td>
</tr>
</tbody>
</table>
### Table 2: Summary displaying drugs/bioactives, disease conditions, and convection methods employed in Convention-Enhanced Delivery (CED).

<table>
<thead>
<tr>
<th>Drug/Bioactive</th>
<th>Disease/Condition</th>
<th>Convection Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal topotecan (Ls-TPT)</td>
<td>Malignant glioma</td>
<td>Vascular targeting-based CED (using reflux-preventing catheters) for liposomal topotecan (Ls-TPT) delivery</td>
<td>[78]</td>
</tr>
<tr>
<td>Topoisomerase I inhibitor CPT-11 (nanoliposomal CPT-11 [nLs-CPT-11]) and PEGylated liposomal doxorubicin (Doxil)</td>
<td>Human glioblastoma multiforme</td>
<td>CED using reflux-preventing catheters</td>
<td>[79]</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Malignant glioma</td>
<td>CED using reflux-preventing catheters</td>
<td>[80]</td>
</tr>
<tr>
<td>Retroviral replicating vectors (RRV) in combination with 5-fluorocytosine (5-FC)</td>
<td>Malignant human glioma</td>
<td>CED using reflux-preventing catheters</td>
<td>[81]</td>
</tr>
<tr>
<td>JCV T-antigen siRNA</td>
<td>Progressive Multifocal Leukoencephalopathy (PML)</td>
<td>CED using reflux-preventing catheters</td>
<td>[82]</td>
</tr>
</tbody>
</table>

**Conclusion**

CED can be used safely and effectively to infuse neurotherapeutics of varying sizes to specific targets within CNS by safely bypassing the BBB. Convective delivery has the potential to produce a homogeneous distribution of solute that may perfuse clinically relevant volumes of CNS at therapeutic concentrations indicating that CED holds a great promise in the management of a various neurological disorders. Either, computer modelled drug delivery to the brain has shown to offer a great assistance in the design of patient-specific drug administration using CED. The desirable outcomes so far obtained with time-reversal acoustics/ ultrasound-assisted CED is a clear demonstration that this technique has the potential to be applied to biomedical situations of ultrasound focusing without the need for complex transducer phased arrays. MRI-guided delivery platform has also proven to allow real-time CED to be performed with a high precision level, and also with a high degree of predictability and safety; an approach that may be highly useful in the improvement of success rate for clinical trials that involve intracerebral drug delivery by direct infusion. In general, the unique features of CED including the ability to monitor distribution in real-time, presents with a great potential for developing new research and treatment paradigms for treating a multitude of CNS disorders.

**Future Perspectives**

The advancement that has been made in molecular technology has culminated into the development of various therapeutic agents for CNS diseases. CED being attributed with the capability of bypassing BBB, may easily deliver neurotherapeutic agents to the extended volumes of brain tissues at the target site. Thus, CED has the potential to serve as a platform that may transform basic molecular findings to clinical settings.

When compared to other therapies, CED is advantageous by the fact that it can expose regional brain tissue to high concentrations of neurotherapeutic agents while minimizing systemic and CNS toxicity. However, much as CED has achieved greater efficacy when compared to traditional delivery methods, it is disadvantaged by the virtue of the fact that it has so far been able to yield insufficient improvements in survival for Phase III clinical trials.

This may certainly be attributed to the limited ability of CED to:

1. Distribute the therapeutic agent uniformly throughout the tumor and
2. Broadly disseminate therapeutic agent to the infiltrative MG cells residing in the primary tumor periphery (not detected by MRI) which correlates with tumor recurrence.

Furthermore, the anatomical heterogeneity of the brain is a major limiting factor during perfusion by CED. For instance, portions of the brain have been found to be inherently
difficult to saturate with drugs due to variations in permeability of white and gray matter, tumor tissue, cerebrospinal fluid tracts and anatomy of vascular beds while the high lipid content of the brain makes predictable movement of aqueous drug formulations a challenge. In addition, traditional catheters lack the arborizing capability to effectively perfuse drug target to distant infiltrative cells. All these deficiencies constitute to the areas that need to be improved in order to increase the CED efficacy, which therefore calls for the need for further/continued research in this area. Otherwise generally speaking, CED has thus far proved to be a novel treatment strategy for brain ailments. Thorough understanding of all CED methods as well as their needful technological improvement may eventually lead to cures of multiple CNS diseases.

Summary

Substantial achievement has been obtained in diagnostic imaging and drug discovery, yet the management of brain diseases like malignant brain tumors has still remained to be a great challenge. The main reason has been the difficultness in crossing the Blood-Brain-Barrier (BBB) for most of CNS therapeutic agents. Apparently it is difficult to obtain effective therapeutic concentrations even for the permeable drugs albeit the fact that maintaining relatively constant/therapeutic drug concentration in the diseased parts of the brain is absolutely important. Delivering of drugs to the CNS is also challenged with the dilemma as to how they can be selectively directed to the discrete anatomic diseased regions of the brain. Convection-Enhanced Delivery (CED) has to a great extent proven to circumvent these challenges. CED is a novel drug-delivery technique that uses positive hydrostatic pressure to deliver a fluid containing a therapeutic substance by bulk flow directly into the interstitial space within a localized region of the brain parenchyma. Principally the technique involves a stereotactic placement through cranial burr holes of several catheters into brain parenchyma and the subsequent infusion of a neurotherapeutic agent via a microinfusion pump directly to the brain thus by-passing the BBB. The method avoids the systemic toxicities of orally administered neurotherapeutics to the brain. CED has now become a frequent treatment option in the management of brain tumors and more recently gene therapy (e.g. in Parkinsonism). Benefits of this intracranial drug-transfer technology include a more efficient delivery of large volumes of therapeutic agent to the target region when compared to other standard delivery approaches such as local infusion and biopolymer-based delivery. The experience that has been gathered for more than a decade in trying to make use of CED principles for treating brain diseases (e.g. cancer) will form a potential platform for clinical applications in the future.

References


growth factor receptor-positive brain tumors by means of cetuximab (IMC-C225) dendrimer bioconjugates. Mol Cancer Ther 5: 52-59.


