Anthem

Medical Policy

Subject: Convection Enhanced Delivery of Therapeutic Agents to the Brain
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Description/Scope

This document addresses the convection–enhanced delivery (CED) process for administering antineoplastics and other agents directly into the brain and the surrounding tissue. CED is a delivery technique to bypass the blood brain barrier (BBB) and administer therapeutic agents directly into targeted brain parenchyma or tissue. CED involves one or more catheters stereotactically placed through cranial burr holes into the brain. Antineoplastics or other therapeutic agents are subsequently administered by microinfusion pump.

Position Statement

Investigational and Not Medically Necessary:

Convection-enhanced delivery of therapeutic agents into the brain is considered**investigational and not medically necessary.**

Rationale

Standard methods of delivering drugs to the brain by intravenous infusions of systemic drugs resulted in limited penetration of the central nervous system. It is estimated that less than 1% of a drug administered systemically will reach the brain (Lewis, 2016). It has been noted that different structures within the brain have various interstitial pressures (Lam, 2011). Intraventricular and intratumoral injections were limited as the molecular weight and solubility of the agent impacted the diffusion. As a result, innovative therapies such as CED continue to be investigated.

CED is a highly technical process that involves stereotactic placement of one or more catheters through cranial burr holes directly into brain tumors or tissue. A therapeutic agent is continuously administered through the catheters by a microinfusion delivery system to create a positive pressure gradient at the catheter tip. As the pressure is maintained, it creates fluid convection or flow to supplement diffusion through the extracellular spaces and enhance the distribution of the drug to the targeted area. Other techniques for placement and differing types of intracranial catheters continue to be investigated (Barua, 2014). The goals of CED are to provide homogenous distribution of a therapeutic agent to a larger volume of brain tissue; provide higher drug concentrations directly to the tissue; and to utilize molecules that do not normally cross the BBB.

A majority of the studies on CED involve various antineoplastic agents for a variety of brain tumors (Barua, 2014; Ellingson, 2021; Hall, 2006; Kunwar, 2006, 2007, 2010; Spinazzi, 2022; Thompson, 2023; van Putten, 2022). CED as a means of local disease control has been of particular interest in the potential treatment of malignant gliomas, which often recur within 2 centimeters of the resection cavity following tumor removal. CED can distribute chemotherapeutics up to 3 cm from the catheter tip (Chaichana, 2015). CED has also been utilized in preclinical and early clinical studies for a variety of therapeutic agents for neurodegenerative diseases (for example, progressive multifocal leukoencephalopathy [PML], Gaucher's disease and Parkinson's disease) as well as other neurologic conditions such as epilepsy and aromatic L-amino acid decarboxylase deficiency (Pearson, 2021).

Hall and Sherr (2006) noted an ongoing study using brain phantom gel to determine the best drug delivery system design and a reliable method to test the system. The use of magnetic resonance imaging and other techniques are also being studied to determine effective and accurate real-time assessments of the convective process. Clinical trials and small case series continue to evaluate the appropriate placement of catheters, volume and the specific drug and concentration of drug infused (Kunwar, 2007; Sampson, 2007, 2008; Tanner, 2007). However, the studies have not been conclusive.

Kunwar and colleagues (2006) reported an investigational trial of 53 individuals with malignant gliomas, of which 47 were glioblastoma multiforme (GBM). A total of 51 participants received CED-infused cintredekin besudotox (IL13-PE38QQR) as a single infusion after resection or sequentially by intratumoral treatment followed by resection and subsequent intraparenchymal infusion. Adverse events were reported in all 3 phases (pre-CED; peri-CED; and post-CED), which sometimes were related to placement of the catheters and sometimes were related to the instillation of cintredekin besudotox. Side effects included headaches, sensory disturbances and hemiparesis.

Kunwar and colleagues (2010) reported results of a phase 3 multicenter study of 296 participants randomized to either postoperative intraparenchymal cintredekin besudotox (CB) or gliadel wafer (GW) to treat first recurrence of GBM. There was no significant difference in the primary endpoint of overall survival (OS). The median survival for CB was 9.1 months and 8.8 months for GW ($p=0.476$; hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.67-1.18). There were no statistically significant differences between cohorts for adverse events (AE) except for a higher incidence of vascular disorders ($p<0.001$). The predominant vascular AE was due to the rate of pulmonary embolism in the CB group compared to the control group (8% vs. 1%, respectively; $p=0.014$). The actual distribution of the drug was not evaluated in this trial.

A retrospective analysis of catheter positioning and drug distribution utilizing computer software that was not available during the phase III PRECISE trial was performed by Sampson and colleagues (2010). The reviewers were blinded to the identity of the institution and the neurosurgeon responsible for catheter placement. Out of 174 participants with sufficient data, only 49.8% of the catheters placed met all criteria for positioning. The investigators also noted from simulations that the amount of target tumor tissue covered by adequately placed catheters was small. The authors concluded additional trials were necessary to determine optimized CED catheter placement; verification of drug delivery and distribution along with safety and effectiveness (Sampson, 2010).

In a review by Lam (2011) "CED has remained experimental due to difficulties in guaranteeing infusate delivery." Clinical trials continue to study the actual hardware used to deliver therapeutic agents and the accurate placement of catheters and the real-time management of high concentrations of infusate to the targeted areas. Additionally, various therapeutic agents to treat diseases affecting the brain continue to be investigated with CED as a delivery method. Three agents that have received orphan drug designation but have not received approval for manufacturing, IL13-PE38QQR and Trabedersen for malignant gliomas and IL4-Pseudomonas toxin fusion protein IL-4(38-37)-PE38KDEL for astrocytic glioma continue to be studied in clinical trials.

Shahar and colleagues (2012) reported a retrospective analysis of 25 individuals with recurrent GBM at a single institution who were treated with placement of 64 CED catheters. The goal was to describe the "Difficulties and pitfalls" related to the CED procedure, and to report on the intra- and postoperative complications (Shahar, 2012). Participants were treated with one, two or three CED catheters, and the timing and number of surgeries varied. Overall, the CED catheter placement surgeries resulted in the following rates of complications and adverse effects: edema (31%), infections (6.9%), seizures (13.8%), hemorrhage (6.9%) and neurological deterioration (13.8%). In 8 participants (27.6%), mild and reversible neurological deterioration occurred. The authors concluded the complications and morbidity associated with CED catheter placement in individuals with GBM were acceptable and mostly reversible. However, also noted was ongoing development of catheters for CED therapy and the recommendation for collection of comprehensive data to "Provide a better risk-benefit assessment and will help in guiding treatment recommendations and patient selection" (Shahar, 2012).

Halle and colleagues (2019) performed a systematic review to provide an overview of the methodological aspects used in all preclinical and clinical studies published from 2011 to 2016 where CED was used for drug delivery in the treatment of GBM. After excluding articles due to search criteria, only 30 studies focusing on CED for GBM therapy had been published during the 2011 to 2016 timeframe. Of the 30 studies, only 1 study was a clinical study and the remaining 29 studies were conducted on rodents. "This indicates that despite CED being known for over 20 years, it is still mainly used in preclinical studies" (Halle, 2019). The researchers noted that there were no data generated in large brain animal models, despite the fact that successful translation of preclinical results depends on sufficient drug distribution in a large brain. The researchers concluded it was crucial that the same CED protocols as those intended for use in humans are studied in larger animals, such as tumor-bearing pigs, "to overcome the challenges that are faced with translation of promising preclinical CED trials into successful clinical trials."

In a 2009 review, Bidros noted the increased pressure gradient within a tumor versus the normal brain along with the heterogeneity of drug distribution within the tumor itself are potential "Limiting factors in drug delivery by this method." Bos and colleagues (2023) also noted that one of the inherent issues with CED is the difficulty in predicting infusate distribution due to the properties of the tumor tissue. They found that "Especially for recurrent tumors, which have rubbery gliotic boundaries, areas of necrosis, and dispersed islands of rapidly proliferating tissue, optimal target delineation for catheters is challenging."

Investigators continue to research ways to optimize CED technology to deliver drugs to effectively treat conditions affecting the brain. Barua and colleagues (2013) noted "Effective CED depends upon a number of parameters - the diameter of the catheter, the catheter implantation method, the rate of infusion, the physicochemical characteristics of the infusate, and the cytoarchitecture of the targeted brain tissue or structure." Preliminary studies evaluating whether techniques such as intraoperative MRI can be used to improve accuracy in the targeting and placing of the CED cannula are needed (Chittiboina, 2015). However, at this time, due to the paucity of comparative clinical trials, the safety and efficacy of the CED procedure have not been determined.

Currently, there are ongoing phase I clinical trials recruiting individuals with Grade III/IV Glioma for administration of therapeutic agents by CED. The published scientific evidence currently available is insufficient to demonstrate the safety and efficacy of administration of therapeutic agents by CED.

The National Comprehensive Cancer Network® clinical practice guideline (2023) and National Cancer Institute (2023) document for brain tumors do not address the delivery of therapeutic agents with convection enhanced delivery.

Background/Overview

Throughout the body, the walls of all blood vessels are made up of endothelial cells that control passage of substances in and out of the bloodstream. There are small gaps between the cells that allow soluble chemicals to be transported in and out of various tissues via the bloodstream. However, the endothelial cells in the brain are packed very tightly, and block most chemicals and molecules from entering the brain. This effect is also known as the BBB, which protects the central nervous system (CNS). The barrier can be crossed by a variety of mechanisms, including transport systems specific for amino acids or sugars, or for molecules of low molecular weight or appropriate lipid solubility. The BBB presents a challenge in the treatment of brain tumors as the majority of cancer drugs are not able to permeate the BBB as they tend to have a polar structure or are too large in molecular weight (Zhou, 2016).

CED is a novel delivery technique to bypass the BBB and directly treat conditions affecting the brain, such as tumors. CED uses hydraulic pressure to displace interstitial fluid with the infusate, allowing for a homogeneous distribution of small and large molecules over large distances. This is in contrast to a direct injection of a tumor which relies upon diffusion to distribute the drug and results in uneven dispersion of the drug over a limited space (Zhou, 2016). While CED is an improvement over direct injection, there are several issues which need to be addressed in further studies, including evaluating factors which influence distribution volumes and technical concerns such as catheter design.

Definitions

Antineoplastic: Having the properties of killing, or otherwise slowing the growth of, tumor cells.

Blood brain barrier (BBB): A protective mechanism that controls the passage of substances from the blood into the central nervous system.

Convection: The movement of fluids based on different characteristics between one area and another, such as a pressure gradient.

Parenchyma: The functional parts of an organ in the body.

Stereotactic: A method used in neurosurgery and research for locating points within the brain utilizing an external, three-dimensional frame of reference usually based on a 3-dimensional coordinate system.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the procedure codes listed below for all applications, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

64999	Unlisted procedure, nervous system [when specified as stereotactic placement of infusion catheter(s) in the brain for delivery of therapeutic agent(s)]

ICD-10 Procedure

00H033Z	Insertion of infusion device into brain, percutaneous approach [when specified as catheter for convection enhanced delivery of therapeutic agent]

ICD-10 Diagnosis

All diagnoses

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Websites for Additional Information

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Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, References and Websites for Additional Information sections.
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