CLINICAL STUDY - PATIENT STUDY

Convection-enhanced delivery catheter placements for high-grade gliomas: complications and pitfalls

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Abstract Convection-enhanced delivery (CED) of compounds into brain tumors reportedly circumvents the blood brain barrier. CED intends to increase drug delivery to malignant cells, reaching high local therapeutic concentration and decreasing or eliminating systemic side effects. Clinical experience and published data on catheter placement (CP) surgery are scarce. We propose practical and technical guidelines for planning CED based on our experience. We retrospectively analyzed the medical charts and relevant neuroimages of 25 patients following the insertion of 64 CED catheters. The patients were enrolled in at least one of four clinical trials using CED for treating recurrent glioblastoma multiforme in our institution between 2003–2006. Intra- and postoperative complications related to CP surgery and the difficulties and pitfalls of planning were evaluated. There were 29 CP surgeries. Forty-four peritumoral brain tissue catheters were inserted in 16 CP surgeries following tumor resection in 16 patients, and 20 catheters were placed into the tumor in 13 procedures in 10 patients. The lesions were in or near eloquent brain tissue areas in 13 of all CP surgeries. Complications included increased edema (31%), infection (6.9%), bleeding (6.9%) and seizures (13.8%). Significant neurological deterioration occurred in 4 patients (13.8%). Difficulties in adhering to CP surgery guidelines included lesion site (superficial, mesial temporal lobe, proximity to CSF spaces), proximity to eloquent cortical areas, tissue density that interfered with the trajectory, and technical limitations of stereotactic instruments. CED procedures for high-grade gliomas may be associated with surgical morbidity. Adherence to guidelines might be difficult because of lesion site and complicated by brain and tumor tissue characteristics. This should be considered while planning clinical trials that use convection-based technology.

Keywords Stereotactic · Catheter placement · Convection-enhanced delivery · Glioma · Surgery

Introduction

High-grade gliomas (HGGs) are the most common malignant primary intracranial tumor in adults. Despite multimodality treatments, including surgery, radiation and chemotherapy, the prognosis remains poor, with a median survival of approximately 1 year following diagnosis [1]. Factors limiting the success of treatment include the invasive nature of the lesion, intrinsic cellular resistance to most treatment compounds, and the presence of the blood brain barrier (BBB) which limits the passage of drugs into infiltrated brain tissue and subsequently requiring higher drug levels to achieve therapeutic concentration. Local drug delivery methods have been developed in an attempt to increase local drug concentration without intensifying systemic side effects. This includes intracavity direct injection or administration of drugs [2], placement of controlled-release impregnated polymers, such as Gliadel wafers [3], chronic low flow microinfusion [4] or convection-enhanced delivery (CED) [5, 6]. CED results in high-flow micro-infusion and the delivery of macromolecules

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through the extracellular space. It can be distributed over a large brain volume and at relatively homogeneous concentrations [5, 7–10]. CED of various drugs and molecules are currently under investigation for the treatment of malignant brain tumors. Most clinical trials using a CED strategy deliver tumor-specific ligands linked to a bacterial toxin into the tumor or its surrounding infiltrated tissue [11–16]. Other approaches include the delivery of chemotherapeutic agents (e.g., paclitaxel) [17, 18], gene therapy (e.g., HSV-1-tk) [19] and local radiotherapy with a cytotoxic dose of 131I [20]. The treatment potentials of the CED approach have been demonstrated in many preclinical and clinical studies in addition to having been the subject of many publications. Large randomize clinical trials, however, have failed to establish a survival benefit derived from using this approach with different compounds, partly because of technical issues related to suboptimal catheter placement (CP) and poor drug distribution [21].

The clinical experience of CP is limited to a few specialized centers, and our literature search failed to produce any data on complications and technical difficulties associated with it. We performed a relatively large number of CP surgeries and now describe the intra- and postoperative complications as well as the difficulties and pitfalls related to this procedure in order to enhance surgical planning.

Patients and methods

This is a retrospective analysis of prospectively collected clinical and neuroimaging data. This review has been approved by our local institutional ethics board (0608-10 TLV). The study group consisted of 25 patients who underwent a total of 29 CP surgeries that were performed at the Tel Aviv Medical Center Department of Neurosurgery between March 2003 and December 2006. They were all diagnosed as having recurrent glioblastoma multiforme (GBM) and were enrolled in one of four clinical trials using implantation of intracranial catheters for CED. All patients received anticonvulsive medications, high does steroids and prophylactic antibiotic perioperatively and during the treatment period.

The three surgical protocols included implantation of catheters into the tumor prior to resection (using 1 catheter), implantation into the peritumoral brain tissue (using between 2–4 catheters) after tumor resection, and implantation of catheters into the tumor without resection (using up to 2 catheters). All catheters used in the studies were commercially available ventricular catheters that were inserted using supplied stiletto (Medtronic Cardiac/Peritoneal Catheters, Medtronic, CA, USA and Vygon, Norristown, PA, USA). CP planning was based on a current magnetic resonance imaging (MRI) study (gadolinium-

enhanced T1-weighted sequence, 3D SPGR, axial scan) and BrainLab, iPlan® stereotaxy software (BrainLab, Germany). The CP guidelines that were followed [22] specified the distance and depth of catheter tip from pial surfaces/deep sulci (>25 mm), cysts, cavities or the ventricular ependymal layer (>5 mm) and distance between catheters (>20 mm). CP surgeries were performed as frameless stereotactic procedures, and two systems were used for catheter insertion: the Navigus Trajectory Guide system (Image-Guided Neurologics, Melbourne, Florida) before December 2004, and a modified BrainLab stereotactic fixation arm afterwards. CP was done free-handed with the aid of a neuro-navigation system in the first four surgeries. All patients underwent one non-contrast head computerized tomographic (CT) scan immediately after the procedure for the evaluation of the catheter position and surgery-related complications, and another CT 4–7 days later after catheter removal. The CP surgeries and the study patients' characteristics (including methods of insertion and number of catheters placed) are summarized in Table 1.

Results

The 25 patients who underwent 29 CP surgeries included 18 males and 7 females, whose mean age was 54.2 ± 11.8 years (range 28 to 70 years). The mean preoperative Karnofsky performance score (KPS) for the group was 88 ± 12.1 (range 70–100). A total of 64 catheters were inserted in 29 frameless stereotactic procedures. The lesions were in or near eloquent brain areas in 13 of the 29 operations (45%).

One of the patients underwent three separate procedures for two different clinical trials and another patient underwent two separate procedures for the same clinical trial. Forty-four peritumoral brain tissue catheters were inserted in 16 procedures following tumor resection in 16 patients. Twenty catheters were placed into the tumor bed in 13 frameless stereotactic procedures in 10 patients. Surgical resection of the tumor followed the CED treatment period occurred in 6 of the patients.

One catheter was placed per procedure in five (17.2%) surgeries, and one of these patients underwent two separate surgeries for the placement of one catheter each time. Two catheters were placed per procedure in 13 (44.8%) surgeries. Two of these 13 patients were treated more than once: one of them was treated twice, each time with two catheters (numbers 28 and 29 in Tables 1, 2). The other patient was treated three times for two different clinical trails, each time with two catheters (numbers 9, 19 and 20 in Tables 1, 2). In 11 CP surgeries (37.9%) the insertion of three catheters per procedure was performed.

Table 1 Procedure characteristics

Procedure number	Sex	KPS	Age, y	Location	Eloquent cortical area (Yes-1, No-0)	Catheters, n	Method used[a]
1	M	100	38	Parieto-occipital	1	1	0
2	M	80	65	Parieto-occipital	0	1	0
3	M	100	52	Frontal	0	1	0
4	M	100	43	Fronto-temporal	0	2	0
5	F	90	58	Frontal	0	2	1
6	F	70	68	Frontal	1	2	1
7	M	100	47	Frontal	1	3	1
8	M	80	61	Parietal	1	3	1
9	M	100	45	Occipital	0	2	1
10	M	100	47	Temporal	1	3	1
11	M	70	62	Temporal	0	3	1
12	M	80	61	Temporal	0	3	1
13	F	100	60	Parietal	1	2	1
14	F	100	58	Temporal	0	3	2
15	F	90	63	Parietal	1	3	2
16	M	80	70	Occipital	0	2	2
17	M	70	46	Frontal	1	3	2
18	M	100	68	Frontal	0	3	2
19	M	90	45	Occipital	0	2	2
20	M	90	45	Occipital	0	2	2
21	F	70	65	Central	1	2	2
22	M	70	53	Temporal	1	2	2
23	M	80	59	Parietal	1	3	2
24	M	70	64	Parietal	1	3	2
25	F	80	41	Central	1	2	2
26	M	100	28	Parietal	0	1	2
27	M	100	28	Parietal	0	1	2
28	M	100	66	Frontal	0	2	2
29	M	90	66	Frontal	0	2	2
Total					13	64	

KPS Karnofsky performance score

[a] Method used: *0* free-hand guided by neuro-navigation system, *1* the Navigus trajectory guide system, *2* a modified BrainLab stereotactic fixation arm

Twenty-three catheters (35.9%) were inserted using the Navigus Trajectory Guide system in nine procedures (31%) for nine patients. Using the modified BrainLab fixation arm for frameless stereotactic navigation, 36 (56.3%) catheters were inserted in 16 (55.2%) separate CP surgeries for 13 patients. Five catheters (7.8%) were inserted free-hand with the aid of a navigation system in four (13.8%) operations. One patient was operated using both of the systems at different times for different clinical trials, and three patients underwent more than one CP procedure. A single pass of the ventricular catheter was sufficient for placement in all cases, but postoperative CT scan adjustments were subsequently needed following six CP surgeries (20.7%) and involved eight catheters (12.5%). The adjustment involved modification of the catheter depth by pulling the catheter out in all cases by 5–15 mm, depending on the required correction. Three of these eight catheters had been placed using the Navigus Trajectory Guide system (13% of the total number of catheters placed with that system) and the other five catheters had been placed using the modified BrainLab fixation arm (13.9% of the total number of catheters placed with that device). All catheters were used for the delivery of local treatment. Of note, 5 out of 6 procedures requiring adjustment of catheter depth were associated with complications.

The complications and adverse effects for CP surgery included edema (31%), infections (6.9%), seizures (13.8%), hemorrhage (6.9%) and neurological deterioration (13.8%).

Mild, asymptomatic increase of brain edema occurred following nine (31%) procedures and after the initiation of CED treatment. Seven of these nine patients had three catheters and the other two patients had two catheters.

Postoperative meningitis developed after two (6.9%) operations. Rhinorrhea developed following tumor resection surgery and bacterial meningitis was diagnosed one week later in one patient (number 11, Tables 1, 2). The other patient (number 18, Tables 1, 2) developed a CSF leak after catheter removal, and this was followed by severe bacterial meningitis. There was a new onset of seizures in two patients and a worsening of preexisting seizures in two other patients following four (13.8%) procedures.

No hemorrhage was observed following CP surgery. Post-catheter removal CT scans demonstrated hemorrhages in two cases (6.9%). One was an asymptomatic minimal hemorrhage that was noted on the CT scan of a patient who had three CED catheters. The other patient had significant hemorrhage in all three tracts, leading to severe neurological deterioration and an additional systemic complication [pulmonary embolism (PE)], which was eventually fatal. Although the coagulation profile was within the normal range the clinical presentation of hemorrhage and PE may suggest an occult coagulopathy.

Significant neurological deterioration, defined as a decrease in the KPS of more than 20 or permanent neurological deficit, occurred following four CP surgeries (13.8%), including one patient who died within 24 days postoperatively. Mild and reversible neurological deterioration (e.g., transient hemiparesis and dysarthria) occurred following eight surgeries (27.6%). We observed a neurological deterioration—significant as well as mild and reversible in eight of the thirteen CP procedures (61.5%) where the lesion was located in or near eloquent brain areas. Whereas, only four CP procedures (25%) were associated with neurological deterioration when the lesion was located away from eloquent brain areas. Table 2 summarizes all the surgeries and related complications.

Technical difficulties were also encountered while planning and performing CP surgery. Following the resection of superficial frontal and parietal lesions or mesial temporal lobe lesions, it became difficult to adhere to the CP guidelines due to the vicinity of the lesion or its resection cavity to CSF spaces. In addition, the proximity of lesions to eloquent cortical areas would have led to suboptimal placement of the catheters if the CP guidelines were to be followed. We also found that insertion of intratumoral catheters into tumors with firm consistency interfered with the planned trajectory and led to bending or deviation of the catheter from its planned trajectory. Trajectory planning through a craniotomy with underlying artificial dura posed another obstacle for catheter insertion

due to the inability to penetrate that dura with a monopolar probe. In addition, steep insertion angles led to deflection and bending of catheters on the cortical pial surface. As for technical limitations related to stereotactic instruments, we found that real-time modification of catheter insertion was limited (trajectory angles smaller than 25°) while using the Navigus Trajectory Guide system, and that this should be taken into consideration during the planning process.

Discussion

This study includes the largest reported experience with CED CP surgery for HGGs from a single site that focuses on practical and technical issues that should be considered in planning future clinical trials involving CED. CED has been studied in preclinical and clinical settings for more than a decade. Phase I/II and III studies using CED have recently been conducted [2, 6, 11–17, 20, 23], but there are no publications describing CP surgical procedures and associated complications. The current study focused on these procedure-related complications and the results indicated that the morbidity associated with CP for the purpose of CED in HGG patients is acceptable and consists mostly of reversible neurological sequelae.

Not surprisingly, we found a strong associated risk of neurological deterioration following catheter insertion in lesions near or in the eloquent cortical areas. The observed edema and seizures were not directly related to the surgical procedure since these events occurred after the infusion treatment had been started. Edema occurred much more frequently following the insertion of three catheters compared to the insertion of two catheters (63.6 vs. 15.4%, respectively). None of the patients treated with one catheter per procedure developed brain edema.

A limitation of this study is our inability to definitively identify which of the two sequential procedures (tumor resection surgery and CP surgery) gave rise to the described complication. However, the two procedures were separated in time by 48–72 h and in all cases the patient baseline characteristics used for comparison were recorded immediately prior to the CP surgery.

Optimal planning was restricted by regional factors (eloquent areas, superficial tumor, vicinity to resection cavity, CSF space or small volume residual brain tissue). Factors that interfered with placement included steep insertion angle (in particular when the Navigus Trajectory Guide system was used), the use of artificial dura and high tissue density tumors. In addition, adherence to CP recommendations[22] was not always technically possible. We recommend that the limitations we found and describe herein should be taken into consideration during the planning process and the insertion of presently available

Table 2 Description of complications per procedure

Procedure number	Catheter position changes, n	Edema	Bleeding	Seizure	Infection	CSF leak	Days of infusion	Decrease in KPS	Comments
1	0	0	0	0	0	0	7	0	
2	0	0	0	0	0	0	7	10	
3	0	0	0	0	0	1	7	0	CSF leak from catheter site, stopped by suture placement
4	0	0	0	0	0	0	7	0	
5	0	1	0	0	0	0	4	0	Mild increased edema
6	0	1	0	0	0	0	4	0	Mild increased edema
7	0	1	0	0	0	0	4	10	Mild increased edema
8	0	0	0	0	0	0	4	10	
9	0	0	0	0	0	0	4	10	
10	2	0	0	0	0	0	4	10	
11	1	0	0	0	1	1	4	20	Rhinorrhea, meningitis
12	0	0	0	0	0	0	4	0	
13	0	0	0	0	0	0	4	30	Neurological deterioration
14	0	1	1	0	0	0	4	0	Some increased edema, minimal bleeding
15	2	1	0	0	0	0	4	0	Increased edema, temporary worsening of sensory dysphasia
16	0	0	0	0	0	0	4	0	
17	1	1	0	0	0	0	4	10	Increased edema, postoperative transient dysarthria
18	1	1	0	1	1	1	4	0	Increased edema, CSF leak from operative wound on POD 7, meningitis and seizures on POD 10
19	0	0	0	0	0	0	4	0	
20	0	0	0	0	0	0	4	0	
21	0	0	0	1	0	0	4	20	Series of seizures, neurological deterioration, hemiplegia
22	1	0	0	1	0	0	4	10	General neurological deterioration, one seizure, back to baseline within 14 days
23	0	1	0	0	0	0	4	0	Increased edema
24	0	1	1	0	0	0	1.5	20	Hemiplegia on POD 2. Hemorrhage in catheter tract following early catheter removal. Pulmonary embolism and IVC filter. Exitus POD 24
25	0	0	0	1	0	0	4	10	New mild left hand clumsiness 7 days post treatment: series of seizures, new plegia of upper limb
26	0	0	0	0	0	0	4	0	
27	0	0	0	0	0	0	4	0	
28	0	0	0	0	0	0	4	0	
29	0	0	0	0	0	0	4	0	
Sum	8	9	2	4	2	2		12	

KPS Karnofsky performance score, *POD* postoperative day, *IVC* intraventricular catheter

catheters. Currently there are a number of modified catheter prototypes in development to overcome the existing limitations of CED therapeutic modality (personal communication). More comprehensive data collected from a larger patient population will provide a better risk–benefit assessment and will help in guiding treatment recommendations and patient selection.

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