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CONVECTION ENHANCED THERMO-CHEMOTHERAPY CATHETER SYSTEM: PRE-510(K) CLEARANCE PROTOCOL DEVELOPMENT: FLUID PERFORMANCE TESTING

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ABSTRACT

Our lab is developing a novel device, the convection-enhanced thermo-chemotherapy catheter system (CETCS), to improve drug dispersal around a glioblastoma. To help prepare the device for clinical trials, we were advised to first prepare and receive 510(k)-clearance. The 510(k)-clearance process includes proving the novel device is substantially equivalent to a previously cleared predicate device. For the CETCS device, we have identified the Cleveland Multiport Catheter (CMC) as our predicate device. In this work, we test infusion pump flow rate, high-pressure flow rate, and microneedle tip deflection; each with respect to infusion and aspiration. The CMC's 510(k) summary sheet provided guidelines for the test protocols to follow. If the CMC's 510(k) summary did not state a metric, we set the metric based on the CETCS device specifications. Replicating or exceeding the threshold passing criteria set by the CMC device or the CETCS specifications demonstrates that CETCS is substantially equivalent to the predicate device for those specific metrics.

Keywords: Convection-Enhanced Delivery, 510(k) Clearance, Predicate Device, Flow Rate, Infusion, and Aspiration.

1. INTRODUCTION

1.1 Glioblastomas and Treatment

Glioblastomas comprise over 13,000 annual cases of central nervous system brain tumors [1-3]. This type of tumor is arduous to treat due to several factors: spider-like extensions of the tumor into healthy brain tissue, high vascularity, the blood-brain barrier, and an inability to visualize the tumor margins with industry-leading imaging techniques. All factors contribute to the noncurative nature of this tumor, despite the standard of care, including tumor resection, radiation, chemotherapy, and often a combination of these three forms of treatment. Furthermore, palliative care is the treatment route taken by many physicians. Unfortunately, this leads to a 5-year survival rate for Glioblastomas being less than 5% [3].

Given the low 5-year survival rate, there is a need to explore alternative approaches, including new methods for local therapeutic delivery. The work presented here focuses on characterizing a device that improves the delivery of therapeutics into the patient's brain. This method ideally will improve the coverage of the target tumor regions.

1.2 Convection-Enhanced Delivery

Convection-enhanced delivery (CED) is an experimental approach pioneered and reported by Bobo *et al.* in 1994 [4], which operates using a pressure gradient to deliver the therapeutics directly into the brain. For instance, a catheter inserted into a patient's brain through a burr hole can facilitate CED [5-6]. By infusing directly into the brain, CED can overcome the blood-brain barrier, a limiting factor for chemotherapeutics delivered systemically throughout the body. Over the years, many types of catheter designs have aimed to optimize the infusion of therapeutics into the brain tissue by providing increased coverage of the tumor [5-6]. However, most of these catheter systems are limited to a single outlet port for drug dispersion and require the introduction of multiple catheters into the brain. Improving tumor coverage through various designs includes incorporating several outlets in a single catheter.

1.3 Convection-Enhanced Thermo-chemotherapy Catheter System

Our lab is developing a new device to facilitate CED, the Convection-Enhanced Thermo-chemotherapy Catheter System (CETCS). The CETCS intends to assist physicians in delivering a therapeutic payload to a region of interest: glioblastoma and additional tumor margins. The CETCS device consists of an actuation block, a main cannula, and several microneedles that can actuate outside of the main cannula and into the tumor and

tumor margins through a set of polyimide guide tubes seen in Figure 1.

In clinical use, the surgeon will insert the CETCS cannula through a burr hole created before infusion and secure the cannula's position using commercially available neuro fixation systems. After fixing the cannula, the surgeon can control the placement of the microneedles, independent of one another. The actuation block allows for control of each microneedle. Each microneedle can be inserted into the brain up to 3 cm past the main cannula at a fixed angle of about 26°. The actuation block provides the surgeon with control of each individual microneedle's placement. This level of control promotes optimal coverage of the target areas of the tumor. A schematic of microneedles in the deployed state are shown in Figure 1.

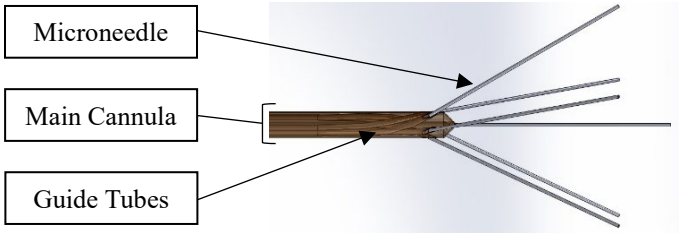


FIGURE 1: MAIN CANNULA WITH DEPLOYED MICRONEEDLES.

1.4 Regulatory Pathway - 510(k) Clearance

Our end goal is to test the CETCS device in clinical trials, which requires institutional review board (IRB) approval at the study sites. The IRBs will require safety testing, such as biocompatibility, sterility, and mechanical performance testing prior to approving the clinical trial at their site. Our regulatory advisor suggested we conduct our safety testing by following protocols outlined by existing predicate devices, and that would allow us to obtain US Food and Drug Administration (FDA) 510(k) clearance of our device along the way. Having FDA regulatory clearance will improve our likelihood of IRBs permitting clinical trials with our CETCS device.

1.5 Predicate Device - Cleveland Multiport Catheter

The Cleveland Multiport Catheter (CMC) is an existing FDA-cleared device that is similar to both technology and intended use with the CETCS device. The indication for use for the CMC is to gain access to the ventricles of the brain for the removal of cerebrospinal fluid or to inject Cytarabine. This catheter system has a main cannula and four microcatheters within a sheath. The cannula is inserted as a single catheter and utilizes a catspaw technique to retract the outer sheath, which exposes the four microcatheters to the brain tissue. In preparation for their FDA submission, CMC researchers conducted three categories of performance tests: flow testing, mechanical strength testing, and tests for how well the device would perform in a clinical environment.

2. MATERIALS AND METHODS

The FDA 510(k) clearance process requires demonstration that a new device is substantially equivalent to an existing identified predicate device. An important aspect of proving our CETCS device is substantially equivalent to the CMC is by conducting similar tests to what the CMC used to demonstrate that they were substantially equivalent to their predicate device. This paper presents the flow tests that show our device is substantially equivalent to CMC with regard to that category of testing. The relevant subcomponent of the CETCS device evaluated in these tests is the microneedles.

2.1 Infusion Pump Flow Rate Testing

For CMC testing it was determined that water mimics the flow of cerebrospinal fluid, since it also has a density of about 1 g/mL [7]. The CMC performance testing also used water as a substitute for cerebrospinal fluid. A single microneedle (Polymicro Molex; polyimide coated capillary tubing, non-light guiding; ID-150 µm/OD-360 µm; TSP150375) was connected to a syringe (BD Syringe; Luer-LokTM Tip; 3 mL; 309657). The syringe was then inserted into an infusion pump (Harvard Apparatus, PHD Ultra; D-401671). Throughout the experiment, a graduated cylinder was placed at the distal end of the microneedle and placed in a mass balance (Mettler Toledo; XS104; B514791800; d = 0.1 mg).

2.1.1 Infusion

For the CMC, a single microcatheter infused a 4.93 mL/hr flow rate while maintaining a pressure under 25 psi. The infusion pump controls the flow rate. Here, we set the flow rate to 0.82 and 4.93 mL/hr and evaluated it over a 30-minute time period, with n = 3. The 0.82 mL/hr represents all six needles being used to reach the 4.93 mL/hr flow rate. A covered beaker collected water on the distal end of the microneedle during the infusion, preventing water evaporation. At time points, the infusion was paused, noting the infused volume on the pump, time, and the beaker weight. These values helped determine the volume collected and the measured flow rate. The pressure was monitored using 30 psi strain gauge pressure sensor (Honeywell; Miniature Low-Pressure Sensors, 26PC Series; 30 psi; 26PC6DF6G) that were read using Labview.

2.1.2 Aspiration

In the CMC 510(k) summary, the CMC device reported a removal rate of 1.7 mL/hr. However, there was no pressure given. The CETCS device was set to aspirate water at the same flow rate, 1.7 mL/hr using the infusion pump. By aspirating at the same flow rate, we can determine the actual flow rate of aspiration as well as the maximum aspiration pressure for the CETCS device. If there is any microneedle movement or the pressure reaches above 25 psi, then the test will be noted as a failure. The 25 psi limit is based on the given value that CMC

was able to maintain infusion under 25 psi. The pressure limit for infusion will also be used for the aspiration pressure limit.

2.2 High Pressure Flow Rate Testing

For the high-pressure flow rate testing, the infusion pump is able to administer a high controlled flow rate. This test can identify how the microneedle responds to a high-pressure event. Water is the chosen medium, due to the similar fluid properties to cerebrospinal fluid. A single microneedle connects to a syringe, and the infusion pump controls the flow rate. The pressure was monitored using 250 psi strain gauge pressure sensor (Honeywell; Miniature Low-Pressure Sensors, 26PC Series; 250 psi; 26PC6GF6G) that were read using Labview.

2.2.1 Infusion

For the infusion experiments, the flow rates evaluated were 10 and 33 mL/hr. These values are two and three-fold times the anticipated flow rates, as set by the CMC and our device specifications. Throughout the infusion, the pressure is monitored using a pressure sensor and a 3-way luer connector between the syringe and the microneedle. The duration of the experiment was 30 minutes, and volumes were determined at several time points using the weight of the graduated cylinder placed at the distal end of the microneedle to collect water.

2.2.2. Aspiration

For the aspiration experiments, the flow rates evaluated were 10 and 33 mL/hr. A filled graduated cylinder sat at the distal end of the microneedle. Throughout the experiment, the microneedle aspirated water out of the graduated cylinder.

2.3 Microneedle Tip Deflection

Figure 2 shows the experimental setup. Here, the pressure the pressure was increased incrementally until it reached 75 psi, and it was held, then 150 psi, held, and then 250 psi, held, and finally the pressure was released and then aspiration started until the pressure read about -13 psi and held. At the conclusion of the experiment, the pressure was relaxed to about 0 psi. A movement larger than 0.5 mm indicates a failed outcome of the test. Evaluation of the images was done using ImageJ software [8].

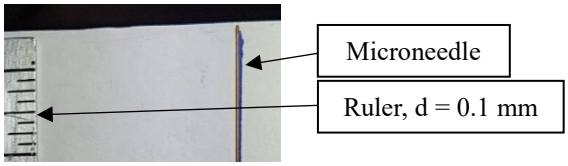


FIGURE 2: EXPERIMENTAL SETUP FOR THE TIP DEFLECTION ANALYSIS OF THE MICRONEEDLES

2.3.1 Infusion

Evaluation of microneedle tip deflection included a microneedle plugged at one end using medical-grade epoxy (EA M-31CL, Henkel Corporation, Dusseldorf, Germany). The pressure sensor and the syringe connect via a 3-way luer connector, primed with 1.5 mL of water. The third connection is the plugged microneedle. The syringe was then placed into the infusion pump and pressure was applied in steps by infusing via the forward motion of the pump. The pressure is applied until it reaches over 75, then over 150, and then over 200 psi. The microneedle was placed on a sheet of paper with a blue line marking to determine if the microneedle strayed from the original positioning. If the microneedle moves more than 0.5 mm in response to the change in pressure, then this will be noted as a failed performance test. For these tests, the CMC group did not report a metric for failure, so we decided that the CETCS device should be limited to 0.5 mm of potential movement.

2.3.2. Aspiration

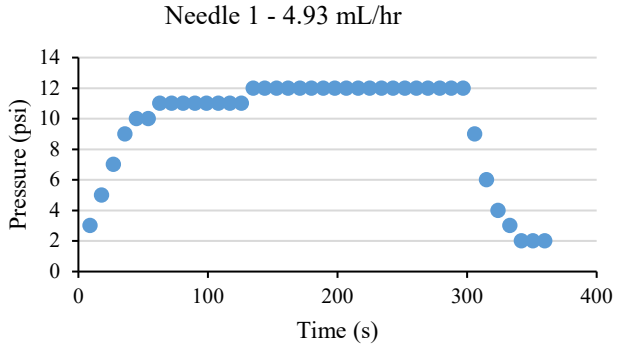
For aspiration, the experimental setup from the infusion experiments is followed. Aspiration in a plugged microneedle is achieved by applying the backward motion of the pump. Like the infusion experiments, if the microneedle moves over 0.5 mm in response to a change in pressure, then this will be noted as a failure.

3. RESULTS AND DISCUSSION

3.1 Infusion Pump Flow Rate Testing

3.1.1 *Infusion*

The measured pressure over time is shown in Graph 1. For all runs, the pressure ramped up to the max pressure. In needle 1 the max pressure measured was 12 psi. The fall in the graph represents the time point where the infusion pump was paused, and the graduated cylinder was weighed. Measurements were taken every 5 minutes. Graph 1 is over a single 5-minute time period for Needle 1 during the 4.93 mL/hr infusion flow rate. For all the experiments, measurements were taken at 5-minute increments.



GRAPH 1. PRESSURE MEASURED DURING FLOW EXPERIMENTS; NEEDLE 1, 4.93 mL/hr

The value of the measured flow rate and the average maximum pressure measured for the infusion experiments are in Table 1. The average maximum pressure is the average of the max pressure measured for each needle, n = 4 (for 0.82 mL/hr, n = 3).

TABLE 1. MEASURED FLOW RATES AND MAX PRESSURE DURING INFUSION (n = 4; *n = 3)

Set Flow Rate (mL/hr)	Measured Flow Rate (mL/hr)	Average Max Pressure (psi)
0.82	0.78 ± 0.14	3 ± 1.7*
4.93	4.97 ± 0.17	11.3 ± 0.5

The CMC device reported an infusion flow rate of 4.93 mL/hr per channel while maintaining an internal pressure below 25 psi. The CETCS device can achieve this flow rate and stay below the set pressure threshold.

3.1.2 *Aspiration*

The aspiration flow rate was set to 1.7 mL/hr. The distal end of the microneedle was inserted into a filled graduated cylinder. The weight was taken at several time points and volume was determined. Table 2 shows the flow rates and maximum pressure.

TABLE 2. MEASURED FLOW RATES AND MAX PRESSURE DURING ASPIRATION (n = 4)

Set Flow Rate (mL/hr)	Measured Flow Rate (mL/hr)	Average Max Pressure (psi)
1.7	1.64 ± 0.28	-3.5 ± 0.6

The CMC testing concluded that a microcatheter can aspirate at a rate of 1.7 mL/hr. The CETCS microneedle followed suit and can aspirate 1.7 mL/hr while maintaining a pressure of 4 psi. Given the pressure is the same amount for the infusion, it is safe to assume the CETCS microneedles are as safe and effective as the CMC microcatheters.

3.2 High Pressure Flow Rate Testing

3.2.1 Infusion

High pressure testing showed the max pressure for a microneedle undergoing a 10 mL/hr infusion is 22 psi, which is still below 25 psi and suggests outperformance of the CMC. In addition, a flow rate of 33 mL/hr resulted in a max pressure of 73 psi. Results are reported in Table 3.

TABLE 3. MEASURED FLOW RATES AND MAX PRESSURE VALUES DURING INFUSION (n = 4)

Flow Rate (mL/hr)	Measured Flow Rate (mL/hr)	Average Max Pressure (psi)
10	9.77 ± 0.32	21.5 ± 0.6
33	32.96 ± 0.60	73 ± 1.4

2.2.2. Aspiration

The pressure for the CMC aspiration experiments is unknown, but they did report the device has an aspiration flow rate of 1.7 mL/hr. For high-pressure evaluation, we evaluated aspiration rates of 4, 10, and 33 ml/hr. The results for these experiments are reported below in Table 4. The CETCS microneedle's flow rate surpasses the reported aspiration rates of the CMC device.

TABLE 4. MEASURED FLOW RATES AND MAX PRESSURE VALUES DURING ASPIRATION (n = 4)

Flow Rate (mL/hr)	Measured Flow Rate (mL/hr)	Average Max Pressure (psi)
4	3.96 ± 0.22	- 8
10	9.88 ± 0.61	- 12.5 ± 0.6
33	32.96 ± 0.22	- 14

3.3 Microneedle Tip Deflection

3.3.1 Infusion

All movements were less than 0.5 mm, which suggests the CETCS' microneedles response to an applied pressure was minimal and the CETCS behaves similarly to the CMC device. The largest movement from the original placement of the microneedle occurred in needle 3, 0.3 mm. Since this is less than our allowed amount of movement, the test is marked as passed fluid performance test.

3.3.2. Aspiration

Aspiration experiments were conducted with infusion experiments. High pressure was applied for aspiration on a plugged needle. Again, there was a minimal movement in the microneedles when the aspiration began. The largest movement during aspiration was 0.1 mm.

4. CONCLUSION

The fluid performance test results presented in this paper suggest the CETCS device is substantially equivalent to the CMC device. Further testing will be conducted to confirm the CETCS is substantially equivalent to the CMC device with regard to mechanical strength and clinical performance.

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