Filtration of SAH via Spinal Catheter

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KEYWORDS: Subarachnoid hemorrhage, lumbar drain, Neurapheresis, cerebrospinal fluid filtration, aneurysm

ABSTRACT: Background and Importance: The amount of subarachnoid blood and the presence of toxic blood breakdown products in the cerebrospinal fluid (CSF) has long been associated with poor outcomes in aneurysmal subarachnoid hemorrhage (aSAH). The Neurapheresis™ system has been developed to filter CSF and remove blood products and is being investigated for safety and feasibility in the ExtracorPoreal Filtration of Subarachnoid Hemorrhage via Spinal CAtheteR (PILLAR) study. We report the first case using this novel device. Clinical Presentation: A 65-year-old female presented with a ruptured left posterior communicating artery aneurysm. Following placement of a ventriculostomy and coil embolization of her aneurysm, the patient underwent placement of a lumbar dual lumen catheter for CSF filtration as part of the PILLAR study. In this case, a total of 9 hours of filtration during 31 hours of catheter indwelling resulted in 309.47 mL of processed CSF without complication. CT images demonstrated an interval reduction of SAH immediately after filtration. The patient was discharged home on post-bleed day 11 and at 30 days showed good recovery. Conclusion: Safety of the Neurapheresis procedure was confirmed in this first case, and we will continue to evaluate safety of the Neurapheresis system through the PILLAR trial.

BACKGROUND AND IMPORTANCE

Aneurysmal subarachnoid hemorrhage (aSAH) is a catastrophic result of a ruptured aneurysm. There are roughly 30,000 cases/year in the US, with worldwide incidence between 4.2-22.7 people per 100,0001.

Blood and blood breakdown products (BBP) in the subarachnoid space (SAS) have long been associated with complications leading to poor outcomes after aSAH, including vasospasm, microthrombosis, and delayed cerebral ischemia (DCI)2–4. Hemolysis of red blood cells (RBCs) in the cerebrospinal fluid (CSF) results in release of hemoglobin which triggers oxidative reactions, neuroinflammation, depletion of nitric oxide, and disruption of the blood brain barrier5–8.

There have been a number of studies on removal of blood and BBPs via lumbar drain (LD)9–12. However, LDs are not broadly used in this patient population. A system that removes blood and BBPs from the CSF more quickly and efficiently may reduce delayed complications following aSAH. We introduce the Neurapheresis™ therapy system (Minnetronix, Inc., St. Paul, MN), an investigational lumbar dual lumen catheter and filtration system designed to rapidly remove blood from CSF. CSF is simultaneously removed via proximal fenestrations (lumbar cistern) and returned post-filtration into the patient through distal fenestrations (mid-thoracic). This case report represents the first in the ExtracorPoreal Filtration of Subarachnoid Hemorrhage via Spinal CAtheteR (PILLAR) safety study.

CLINICAL PRESENTATION

A 65-year-old female and presented to an outside hospital after a thunderclap headache. An external ventricular drain (EVD) was placed and the patient was transferred. On admission, Glasgow Coma Scale was 14, World Federation of Neurosurgical Societies (WFNS) 2, Hunt-Hess (HH) 3. She had neither family history of aSAH or cerebral aneurysm.

A brain CT showed diffuse aSAH (modified Fisher Grade 3); CTA demonstrated a left posterior communicating artery aneurysm confirmed by angiography (7.3 x 4.6 x 2.9 mm) as a wide neck aneurysm. Informed consent for PILLAR was obtained from a legally authorized representative. The aneurysm was secured via coil embolization (Raymond Class 2).

Neurapheresis catheter placement began at 18 hours post-bleed immediately following coiling. Entry was at L3/L4, and fluoroscopy provided visual confirmation of CSF access and spinal level. The guidewire and catheter were placed without complication, and final placement was verified on fluoroscopy with the proximal radiopaque marker bands at L2/L3 and distal marker bands at T1 (Figure 1). A successful filtration flow test

This article has been accepted for publication in Operative Neurosurgery Published by Oxford University Press.
was performed and the catheter was secured using a StayFIX® (Merit Medical), Tegaderm™ (3M), and tape.

Neurapheresis filtration was initiated at a flow rate of 0.5 mL/min for the first two hours of pump time and steadily increased until reaching a maximum of 0.8 mL/min and paused during lumbar CSF sampling, or when ICPs were less than 5 mmHg, as directed by the physician. After 9 hours 9 minutes of filtration, 309.47 mL of CSF was processed. Protein levels in the CSF decreased by greater than 5-fold (Figure 2) and CSF RBCs decreased from $5.45 \times 10^5$ to $4.88 \times 10^5$ cells/µL. Notably, the RBC measurement proved variable due to sampling technique, RBCs settling in coiled tubing, and pump duty cycling. Using system parameters and CSF RBC counts, an estimated 35.2 mL of whole blood was removed from CSF via filtration.

During filtration, the EVD was clamped and ICP was transduced continuously. ICPs were recorded hourly into the EMR per standard of care (SOC). There did not appear to be a direct relationship between pump time and ICP, though continuous ICP measurement would need to be obtained for comparison (Figure 3).

FOLLOW-UP AND OUTCOMES:

Post-filtration, the patient remained in the Neuro ICU until discharge. TCD data was collected at regular intervals and a 7-day angiogram and CT scan were performed (Figure 4). There was no clinical vasospasm and only mild angiographic vasospasm, potentially triggered by the initial hemorrhage or unfinished filtration of the CSF, due to protocol restrictions. Analysis of pre- and post-filtration CTs showed an interval decrease in cisternal blood, denoted by a drop in the Hijdra Score from 30 to 10. The EVD was removed on day 7. The patient was discharged home on day 11 post-bleed.

At 30 days, final surveillance found the patient’s mRS score stable at 2, Glasgow Outcome Scale score of 5, and Barthel Index of 95.

DISCUSSION:

Despite modern treatments, persistent disability and poor outcome occurs in 20-55% of patients that survive aSAH. Studies report clinical vasospasm in 18-63%, with vasospasm-related DCI ranging from 13%-54%. The percent of patients who go directly home after discharge ranges from 25% to 57%, and 6-month mortality is between 2.1-15%. Reducing late morbidity and mortality related to neuroinflammation, clinical vasospasm, DCI, and hydrocephalus remains a top priority.
LDs are ubiquitous in neurocritical care and have been shown to reduce the incidence of clinical vasospasm in aSAH patients by as much as 40% compared to controls\textsuperscript{8,11}. Several attempts have been made to confirm these results, the most recent being the EARLYDRAIN study in which results are pending\textsuperscript{20}. Despite promising outcomes, the EVD remains the more popular device for hydrocephalus management.

Current LDs are hampered by long, inefficient, and manual periods of drainage, but closed loop CSF filtration via the Neurapheresis system may provide rapid, efficient, and controlled removal of hemorrhagic blood and BBPs from the CSF in aSAH, prior to downstream effects. This system can theoretically remove the target particles from CSF faster than LD, where net drainage is limited by natural CSF production rate.

The PILLAR study is a 15 patient, non-randomized, multicenter, first-in-human feasibility, US safety trial. Patients are eligible with aSAH and modified Fisher grade 2, 3, or 4, HH grade I-III, and WFNS Grade I-IV (See Table 1. for Full Inclusion/Exclusion Criteria). The Neurapheresis catheter must be inserted immediately after Neurapheresis therapy, and (C) at 7-day follow-up.

This report details the first patient in the PILLAR trial to receive Neurapheresis therapy. CSF filtration was performed for 9 of the 31 hours of indwelling time without complication. There are several advantages to closed loop filtration over LD. First, a filtration system can theoretically remove target particles from the CSF faster, rather than depend on the natural rate of CSF production to slowly drain hemorrhagic CSF. Because the system returns filtered CSF, having removed all cells (e.g. RBCs) and most proteins, it can circulate this and potentially provide much more rapid clearance of blood volume. In addition, return of CSF back to the patient post-filtration may help reduce overdrainage complications encountered with traditional LDs.

It is well known that a significant volume of blood can exist in the lumbar space, escaping detection on Head CT. This pooled blood in the lumbar space will likely be more amenable to clearance with LD than EVD. However, the ability of a filtration device to affect the resolution of blood in the brain is unknown; we interpret, in this report, the drop in Hidra score, proteins, and RBCs as blood being mobilized caudally and anticipate further clearance of RBCs with longer pump times. This will continue to be investigated in this and subsequent trials to interpret results contextually versus SOC.

CONCLUSION

In conclusion, this is the first case report of an aSAH patient undergoing Neurapheresis therapy as part of a clinical trial. Enrollment and data collection are ongoing for this Phase I trial.

REFERENCES


### Table 1. PILLAR Study Inclusion and Exclusion Criteria

This table shows the inclusion and exclusion criteria for the PILLAR study.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Age: 18 years or older</td>
<td>Patients with a SAH due to mycotic aneurysm or AV malformation</td>
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<tr>
<td>Informed consent by the patient or his/her legally authorized representative</td>
<td>Patients who present with an acute MI or unstable angina</td>
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<tr>
<td>Modified Fisher Grade 2, 3, or 4</td>
<td>Patients with uncontrolled diabetes</td>
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<tr>
<td>Hunt &amp; Hess I-III</td>
<td>Patients who present with a creatinine &gt; 2.0mg/dl</td>
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<tr>
<td>First aneurysmal SAH that has been confirmed by Angio, CTA or MRA</td>
<td>Imaging demonstrates supratentorial mass lesions greater than 50 cc</td>
</tr>
<tr>
<td>Patient is ≤ 36 hours post bleeding event</td>
<td>Imaging demonstrates more than 5 mm of mid-line-shift associated with infarction and or edema</td>
</tr>
<tr>
<td>World Federation of Neurosurgeons (WFNS) Grades I-IV and those Grade V patients who improve to Grade IV or less after ventriculostomy.</td>
<td>Effacement of the basilar cisterns (suprasellar, ambient, chiasmatic and quadrageminal)</td>
</tr>
<tr>
<td>Vasospasm on admission as defined by angiographic evidence</td>
<td>Patients with a coagulopathy that cannot be reversed per the professional discretion of the investigator</td>
</tr>
<tr>
<td>Patients with a documented history of cirrhosis</td>
<td>Thrombocytopenia def. platelet count &lt; 100,000</td>
</tr>
<tr>
<td>Patients who will be managed with supportive care rather than intervention</td>
<td>Patients on low molecular weight heparin e.g., Lovenox</td>
</tr>
<tr>
<td>Obstructive hydrocephalus i.e., non-communicating</td>
<td>Patients on Clopidogrel bisulfate (Plavix) or other chronic platelet inhibitors</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Patients with a documented history of cirrhosis</td>
</tr>
<tr>
<td>History of posterior fusion hardware that would interfere with placement of the catheter</td>
<td>Obstructive hydrocephalus i.e., non-communicating</td>
</tr>
<tr>
<td>Local skin infections or eruptions over the puncture site</td>
<td>Pre-existing Lumbar Drain</td>
</tr>
<tr>
<td>Signs of systemic infection/sepsis or pneumonia</td>
<td>Lumbar puncture within 6 hours</td>
</tr>
<tr>
<td>Lumbar puncture within 6 hours</td>
<td>Concurrent participation in another study which is not observational or retrospective in nature without prior approval from the Sponsor</td>
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