**Results**

Overall, numerical and in vitro results showed agreement in terms of spatial-temporal concentration of tracer over the 24-hour simulation period. Neurapheresis therapy was found to clear tracer from the CSF more rapidly than lumbar drain with most of the clearance occurring within the thoracic SAS after 1-hour of treatment.

***Geometric and hydrodynamic parameters***

A summary of volumetric parameters for the model is included in **Table 2**. Total length of the SAS (cranial and spinal) was 75.6 cm. Spinal SAS volume was 100.3 mL and intracranial CSF volume was 221.6 mL. A review of more recent literature using non-invasive MRI-based methods indicates that total CSF volume in healthy adults to range from ~250 to 400 cm3 (48-52). The hydraulic diameter and Womersley numbers had an average value of 6.2 mm and 9.8 within SAS (**Figure 3a**). Local maxima for hydraulic diameter and Womersley number were located at the foramen magnum. Mean CSF velocity had the greatest values in the lumbar spine at -4.7 and 2.8 cm/s for the peak systole and diastole, respectively. Minimum of the mean velocity occurred in the cranial SAS (**Figure 3b**). Mean cross-sectional perimeter and area were 28.3 cm and 4.2 cm2, respectively. As expected, maximum area and perimeter was located at the cranium (**Figure 3c-d**). A notable increase in area and perimeter was present at ~5 cm cranial to the foramen magnum where the lateral ventricles are located. Maximum Reynolds number was 461 and was located at the caudal end of lumbar spine where the in vitro model tubing entered the system (required for the in vitro model flow pump connection) (**Figure 3e**).

**TABLE 2.** CSF space geometric parameters.

|  |  |
| --- | --- |
| Parameter | Volume (mL) |
| Spinal cord | 19.6 |
| Nerve roots | 6.0 |
| Dura | 125.9 |
| **Total Spinal CSF** | **100.3** |
| Cortical SAS | 153.6 |
| Ventricular system | 19.7 |
| Cerebellar SAS | 21.8 |
| Basal cisterns | 26.5 |
| **Total Intracranial CSF** | **221.6** |
| *Total CSF* | *321.9* |

Total Spinal CSF = Dura – (Nerve roots + Spinal cord)

Total Intracranial CSF = Cortical SAS + Ventricular system + Cerebellar SAS + Basal cisterns

***Numerical quantification of steady-streaming CSF velocities and dimensionless parameters***

Neurapheresis therapy was found to have a larger impact on  and  in comparison to lumbar drain. Overall, Neurapheresis therapy resulted in greater steady-streaming velocity magnitude within the region between the return and aspiration ports (**Fig. 4**). The sagittal  velocity profile indicated a large region of caudally directed steady-streaming on the posterior side of the middle thoracic SAS during Neurapheresis therapy.  within this region decreased with lumbar drain. However, steady-streaming remained similar between the two therapies on the anterior side of the cervical SAS. The coronal  velocity profile was of a smaller magnitude and similar in both Neurapheresis therapy and lumbar drain (**Fig. 4a**).  indicated a cranially directed steady-streaming in the left frontal cranial SAS and caudally directed steady-streaming elsewhere. Steady-streaming in the cranial SAS was ~50X smaller than in the spinal SAS for both Neurapheresis therapy and lumbar drain (**Fig. 4b**). Note, to better visualize results along the entire spine, **Fig. 4b** is contracted at ½ scale in the z-direction (maximum spine curvature with respect to the z-axis is <15 degrees). The average value of  between the aspiration and return ports was 60% greater with Neurapheresis therapy (0.37 mm s-1 versus 0.23 mm 1/s for lumbar drain) (**Fig. 4c**).  showed a nearly identical trend as . The average value for  between the aspiration and return ports was 0.040 and 0.025 for Neurapheresis therapy and lumbar drain, respectively (**Fig. 4d**).

The square of the Womersley number and oscillatory Peclet numbers were calculated to estimate the potential enhancement of dispersion by shear. For both tracer and hemoglobin  is 7.84 in the cortical SAS and 67.55 in the spinal SAS. The Womersley number is in the unsteady flow regime in the spinal SAS, but only marginally in the cortical SAS.

 for tracer and hemoglobin is 1.64 E+04 6.84 E+04 in the cortical SAS and 1.41 E+05 and 5.89 E+05 in spinal SAS. The large Peclet numbers indicate that dispersion is unsteady, thus secondary mixing across the cross section can increase axial dispersion.

for tracer and hemoglobin is 6.21 E+06 and 2.59 E+07in the cortical SAS and 7.2 E+05 and 3.0 E+06 in the spinal SAS. Since  is large compared to unity, the effective diffusivity is independent of molecular diffusivity. Therefore  is 0.0026 m2/s in the cortical SAS and 3.0677 E-04 m2/s in the spinal SAS.  number for the tracer and hemoglobin was calculated to be 7.5 E-06 at the cortical SAS and 9.6 E-03 at the spinal SAS, respectively.

***Comparison of tracer concentration***

Baseline tracer concentration was set to 10% throughout the model. After 24-hours, tracer concentration was reduced to 4.9% under Neurapheresis therapy compared to 6.5% under lumbar drain. Tracer clearance in the thoracic region occurred more rapidly after one hour under Neurapheresis therapy compared to lumbar drain (**Fig. 5a1** and **5b1**, Thoracic). There was little difference in the intracranial cross-sectional average tracer concentration for Neurapheresis therapy versus lumbar drain (6.6% in both cases) (**Fig. 5a1** and **5b1**, Head). Cross-sectional average tracer concentration decreased to ~1.5% in the spinal SAS after one hour (**Fig. 5a2**) compared to 6.5% with lumbar drain after 24-hour (**Fig. 5b2**). Spatial-temporal distribution of tracer clearance under Neurapheresis therapy showed that maximum clearance occurred caudal to the return port (z = -15 cm).

The highest deviations between the in vitro and CFD occurred in the cranial region (**Fig. 5a3**). The minimum tracer concentration in the cranial region occurred near the ventricles where the CSF production channels are located (~ z=10 cm). Comparison of spatial-temporal tracer clearance trends with lumbar drain showed nearly identical results for both CFD and in vitro while the clearance rate decreased gradually in caudal direction (**Fig. 5b3**).

2D tracer concentration profiles were relatively uniform around the spinal cord circumference (X and Y directions) under both Neurapheresis therapy (**Fig. 6a**) and lumbar drain (**Fig. 6b**). In contrast, tracer concentration was non-uniform around the brain with local tracer concentration reduction near the cerebellum due to CSF production from the ventricles via the foramen Luschka and Magendie.

***Quantitative comparison of in vitro and numerical simulations***

Overall, the distributions and clearance rates of tracer concentration in Neurapheresis therapy and lumbar drain match the bench-top patterns. Numerical simulations predicted slightly faster clearance rates under Neurapheresis therapy and lumbar drain than in vitro (**Fig. 5**).

Differences between spatial-temporal cross-sectional average tracer concentration over 24-hours obtained from in vitro and CFD were quantified using Bland–Altman plots (**Fig. 7**). A relatively strong linear correlation was observed between the numerical and in vitro results for Neurapheresis therapy (**Fig. 7a1**, = 0.89, slope = 1.01). Linear correlation for the lumbar drain case was moderate (**Fig. 7b1**,  = 0.65, slope = 1.2). The second set of Bland–Altman plots (**Fig. 7a2** and **7b2**) showed that a greater discrepancy between in vitro and CFD results tended to occur for z-positions closer to the cranium. The 95% confidence intervals for Neurapheresis therapy and lumbar drain were +2.13 to -1.93% and +2.29 to -2.69%, respectively (**Fig. 7a2** and **7b2**).