

Guidance for Aspiration and Flush in the CLEAR III Trial

A four milliliter (4 mL) flush was selected because it balances the need for test article distribution with the need for ICP control. Five milliliters of CSF is a small volume usually available for aspiration, yet 4 mL of flush is a large volume capable of spreading the test article by bulk flow to the third and fourth ventricles when the ventricular system is open. In

the closed system, 4 mL of flush allows for substantial dispersion of test article in the periclot region. We realize that aspiration of ≥ 5 mL cannot always be achieved, thus this guidance provides a rationale as to how to proceed when other situations arise.

Guidance

Equipment

Connect the IV drainage tubing to the IVC with a three-way stopcock as the injection port (needle-less system); do not use the IV tubing ports. The following recommendations are based on IVC tubing that is 33 cm in length (internal/external diameter of 1.7 mm/3.0 mm; Medtronic IVC), stopcock dead space of ≤ 0.3 mL, and commonly-related ICP issues during dosing.

Specific situations can vary, especially if your IVC equipment differs significantly from the above measurements. In this is the situation, you should calculate the volume of flush required to ensure intraventricular delivery of the study agent:

$$\text{Volume of a length of tubing: } V = \pi r^2 h$$

(V = volume (mL); π = pi (3.141593); r = radius of internal diameter (mm; radius = $\frac{1}{2}$ diameter); h = height or length of tubing (mm))

Aspiration

In all patients, try to remove 5-10 mL of CSF. Removal of more CSF volume than you need to

replace creates a net reduction of CSF intraventricular volume which may help with maintaining ICP control during the one-hour closure period. And, larger aspirations allow for full flushes which, we believe, produces a wider distribution of test article in the ventricular system.

When less than 4 mL of flush is considered:

When you cannot inject 4 mL flush, inject 3 mL. If you cannot inject 3 mL flush, then inject 2 – 2.5 mL. A minimum of two mL of flush is desired to disperse substantial test article into the periclot region.

If removal of 5 mL CSF cannot be achieved but ICP is controlled, clamp the IVC to accumulate CSF, then retry in 1 hour and use at least 2 mL of flush.

When ICP is high prior to instillation of study agent, establish ICP control before treatment. Once controlled, instillation of study agent (1 mL) is appropriate with at least 2 mL of flush. Use additional medical management to control/maintain ICP; if ICP cannot be controlled, open the IVC at a popoff of 25 mm Hg.

