CLEAR III Clinical Trial

CLEAR III is a 500-patient Phase-III randomized clinical trial using a recombinant tissue plasminogen activator to quickly remove this blood from the ventricles. It is the hope of the over 70 academic medical centers in this international clinical trial that this may prove to be a better way to treat this brain injury.

The primary aim of the study is to determine whether the rapid removal of intraventricular hemorrhage (IVH) with low-dose rTPA improves modified Rankin Scores over 12 months compared to subjects treated with best medical care alone. Earlier studies have shown that placing a small catheter into the ventricle and giving a series of doses of TPA through it can remove most of the blood within a few days. Although it seems logical and early results have been promising, physicians still do not definitively know if removing the blood quickly (as compared to the slow healing process that naturally occurs over a period of weeks to months in patients that initially survive the stroke) will result in a better outcome for the patient 6-12 months later. If this therapy can reduce the rate of death and improve the quality of life for these patients, it could significantly change the way intraventricular hemorrhage is treated around the world.

CLEAR-III is the culmination of 10 years of research over a number of investigational trials. The early clinical studies were supported by grants from the Food and Drug Administration (FDA) Office of Orphan Products Development, the American Heart Association and other organizations. Current funding for CLEAR III is supported by grants from the National Institute of Neurological Disorders and Stroke (NINDS) and from the Eleanor Naylor Dana Charitable Trust, the Jeffrey and Harriet Legum Endowment, and support from Genentech, Inc. Over 70 major hospitals and academic institutions are participating in this trial as clinical sites or support teams.

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Intraventricular tissue plasminogen activator may help lyse clot and maintain intraventricular catheter (IVC) patency or reopen a clotted IVC. However, the trial [1)] showed no benefit of using 1 mg tPA vs. saline for the primary endpoint of mRS score ≤3 at 6 mos for patients with <30 ml clot (lower mortality at 6 mos was offset by a larger number of survivors with mRS = 5).

The Clot Lysis: Evaluating Accelerated Resolution of IVH trial examined whether irrigating the ventricular system with alteplase improved functional outcomes in patients with small intracerebral hemorrhage (ICH) and large intraventricular hemorrhage (IVH).

The primary outcome measure is dichotomized modified Rankin Scale 0-3 vs. 4-6 at 180 days. Clinical secondary outcomes include additional modified Rankin Scale dichotomizations at 180 days (0-4 vs. 5-6), ordinal modified Rankin Scale (0-6), mortality and safety events at 30 days, mortality at 180 days, functional status measures, type and intensity of intensive care unit management, rate and extent of ventricular blood clot removal, and quality of life measures [2)].

Poor outcomes were associated with mass-related obstruction of the third ventricle from thalamic ICH in alteplase-treated patients and from IVH in saline-treated patients. Once the ventricular system is cleared with alteplase, obstruction of cerebral spinal fluid flow from thalamic hemorrhage might become important in functional recovery [3].

Of the 500 patients with IVH, Venous Thromboembolism (VTE) occurred in 59 patients (11.8%) within the first 30 d. VTE chemoprophylaxis was initiated in 412 (82.4%) patients, but before VTE diagnosis in only 401 (80.2%) at median of 4 d (interquartile range, 1-8) from IVH onset, and was not associated with intracranial bleeding or catheter tract hemorrhage. In the multivariate logistic regression analysis, infection within 30 d (odds ratio, 1.80; confidence interval, 1.03-3.17) was significantly associated with higher odds of VTE occurrence. Starting VTE chemoprophylaxis after 72 h was additionally associated with VTE occurrence after the first week.

Infection and delay in the timely initiation of VTE chemoprophylaxis were associated with VTE occurrence. VTE chemoprophylaxis in IVH appears safe and should not be delayed beyond standard care policies for ICH including when intraventricular catheter placement and thrombolytic therapy are performed [4].

Intraventricular thrombolysis marginally increases the overall risk of symptomatic hemorrhagic complications after IVH, and only during the treatment phase [5].

Catheter tract hemorrhage (CTH) incidence on initial catheter placement and during stabilization was relatively low, despite emergent placement in a high-risk population. Catheter placement accuracy was similar or better than convenience samples from the published literature. Decreasing the risk of CTH may be achieved with attention to catheter placement accuracy and placement in the operating room. Antiplatelet agent use was an independent risk factor for CTH [6].

Among patients with spontaneous IVH requiring emergency CSF diversion, those with early elevated intracranial pressure, high CSF output, and placement of more than one EVD are at increased odds of permanent ventricular shunting. Administration of intraventricular alteplase, early radiographic findings, and CSF measures were not useful predictors of permanent CSF diversion [7].

In patients with intraventricular haemorrhage and a routine extraventricular drain, irrigation with alteplase did not substantially improve functional outcomes at the mRS 3 cutoff compared with irrigation with saline. Protocol-based use of alteplase with extraventricular drain seems safe. Future investigation is needed to determine whether a greater frequency of complete intraventricular haemorrhage removal via alteplase produces gains in functional status [8].

Risks of bleeding and infection in the CLEAR III trial are comparable to those previously reported in EVD case series. Rates of new bleeds and bacterial meningitis/ventriculitis are very low despite multiple daily injections, blood in the ventricles, the use of thrombolysis in half the cases, and generalization to >60 trial sites [9].

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