Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomized, multicentre, multiregion, placebo-controlled CLEAR III trial.

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Intracerebral hemorrhage (ICH) with intraventricular hemorrhage (IVH) has devastating neurologic consequences, with a mortality of up to 50% and serious morbidity in survivors. Prior data had suggested that removal of IVH could improve survival and functional outcomes by relieving acute obstructive hydrocephalus and reducing neurotoxicity. Additionally, prior preliminary data suggested that alteplase (tPA) could safely remove clot from ventricles in patients with an extra-ventricular drain (EVD). For this reason, the authors hypothesized that patients with small ICH and large IVH comprised a subgroup of patients where a severe prognosis may be reversible, and that irrigating the ventricles with tPA would improve their functional outcomes; they designed the CLEAR III trial to test this hypothesis.

Experimental Design and Statistics: CLEAR III was a multicenter, prospective, randomized controlled trial performed at 73 sites. Eligible patients were 18-80 years old, within 24 hours of symptom onset, and with diagnosis of obstructive hydrocephalus confirmed via head CT showing IVH with obstruction of the 3rd or 4th ventricle. Patients were included if the ICH was supratentorial at a volume (via ABC/2 method) of ≤ 30 mL, and with clot stability (no measured expansion >5 mL on repeat CT at least 6 hrs after EVD placement). Patients were excluded if they had an MRS ≥ 2, had ongoing coagulopathy, limitations to care, or suspicion for aneurysm, AVM, or other vascular abnormality. Eligible patients were randomly assigned in a 1:1 ratio within 72 hours of ictus. All participants (other than site pharmacists) were masked to randomization. Thereafter, randomized patients received 1mg tPA or 0.9% saline, up to 12 doses at least 8 hours apart, with head CTs every 24 hours. Investigators were asked to remove as much clot as possible until a pre-defined stopping point (IVH mass effect relieved, 3rd and 4th ventricles open on head CT, or 12 doses given) was reached. All patients were otherwise managed using the AHA guidelines for treatment of spontaneous ICH. The primary outcome was mRS ≤ 3 at 180 days.

Results: A total of 500 patients were recruited, with 249 allocated to the tPA group and 251 in the saline group. Baseline characteristics of each group were similar (Table 1). mRS of ≤ 3 was achieved in 48% of patients in the tPA group and 45% of patients in the saline group (p=0.554, Tables 2 and 3). There was a 50% decrease in the odds of death (mRS 6) for tPA vs saline (adjusted OR 0.50, p=0.004), with greater Kaplan-Meier survival probabilities throughout the 180 days of follow up in the tPA group (cumulative case fatality 18% vs 29%; p=0.006; figure 3). However, post-hoc analyses showed a greater proportion of patients with an mRS of 5 in the tPA group (17% vs 9%; p=0.007). Safety factors (bacterial ventriculitis, serious adverse events) favored the tPA group, with similar rates of serious bleeding between the groups. A planned secondary analysis between the amount and timing of clot removal showed a significant relation between amount of clot removal and an improved odds of an mRS ≤3 and case fatality.

Conclusions: Overall, this trial was neutral on its primary outcome; irrigation of the ventricles with tPA in patients with a small ICH with IVH and obstructive hydrocephalus did not improve functional outcomes at 180 days. Though irrigation with tPA did improve survival, most of the patients had severe

disability with an mRS of 4 or 5. tPA was safe compared to saline, and there was an association between volume of clot removal and improved odds of mRS ≤ 3 on secondary analysis. Further investigation could be targeted at whether the volume of clot removal can improve outcomes (and such trials have been proposed), but this trial did not provide strong enough evidence to change clinical practice in the treatment of ICH with IVH.

Summary compiled by Nathan Bicher, M.D.