Resolution of Intraventricular Hemorrhage Varies by Ventricular Region and Dose of Intraventricular Thrombolytic

The Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) Program

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Background and Purpose—The Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) program is assessing the efficacy of intraventricular recombinant tissue-type plasminogen activator (rtPA) for spontaneous intraventricular hemorrhage (IVH). This subanalysis assesses the effect of dose of rtPA by region on clearance of IVH.

Methods—Sixty-four patients within 12 to 24 hours of spontaneous IVH were randomized to placebo or 0.3 mg, 1 mg, or 3 mg of rtPA twice daily through an extraventricular drain. Twelve subregions of the ventricles were scored from 0 to 4. Effect of dose on IVH clearance to 50% of baseline score was compared by survival analysis for all regions combined and by subregion. Models including ventricular region, dose, and baseline score were compared by Cox proportional hazards.

Results—IVH score reduced faster across all regions with increasing rtPA dose (clearance to 50%: log-rank $P<0.0001$; placebo—11.43 days, 95% CI, 5.68–17.18; 0.3 mg—3.19 days, 1.00–5.38; 1 mg—3.54 days, 0.45–6.64; 3 mg—2.59 days, 1.72–3.46). In the combined models, dose and baseline score were independently associated with reduction in IVH score, which was quickest in the midline ventricles, then the anterior half of the lateral ventricles and slowest in the posterior half of the lateral ventricles (clearance to 50%: $P<0.0001$; rtPA dose: hazard ratio, 1.47, 1.30–1.67; midline versus anterolateral hazard ratio, 1.71, 1.08–2.71; midline versus posterolateral hazard ratio, 4.05, 2.46–6.65; baseline score hazard ratio, 0.96, 0.91–1.01) with a significant interaction between dose and ventricular region ($P=0.005$).

Conclusions—rtPA accelerates resolution of IVH. This effect is dose-dependent, is greatest in the midline ventricles, and least in the posterolateral ventricles.

Clinical Trial Registration—URL: www.clinicaltrials.gov. Unique identifier: NCT00650858.

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Key Words: intraventricular hemorrhage ■ randomized controlled trials ■ thrombolysis

Intraventricular hemorrhage (IVH) complicates 40% of intracerebral hemorrhage[1] and increases mortality[2] due to larger associated intracerebral hemorrhage and occlusion of the third and fourth ventricles. However, normalization of intracranial pressure does not reverse the neurological deficit,[3] probably because of direct toxicity of blood products.[4] Recombinant tissue-type plasminogen activator (rtPA) increases resolution of IVH,[5–8] reducing intracranial pressure, duration of cerebrospinal fluid diversion, and direct neural injury. The clinical efficacy of rtPA is being assessed in the The Clot Lysis: Evaluating Accelerated Resolution (CLEAR) III trial. This analysis of the safety[8] and dose-finding phases of the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) program assesses the effect of rtPA dose according to ventricular region (online-only Supplemental Data).

Methods

CLEAR-IVH safety recruited 48 patients aged 18 to 75 years old, who had at least 1 CT scan after insertion of an extraventricular drain (EVD) and started treatment within 12 to 24 hours of a spontaneous IVH.[8] They received 3 mg intraventricular rtPA or placebo twice daily, after which the EVD was clamped for 1 hour. Patients underwent daily CT scans until treatment was completed and a follow-up scan between 28 and 32 days. In CLEAR-IVH dose-finding Phase 1, 16 patients were randomized to 0.3 mg or 1 mg rtPA according to the same protocol. The second phase of this study was excluded due to a different dosing schedule.

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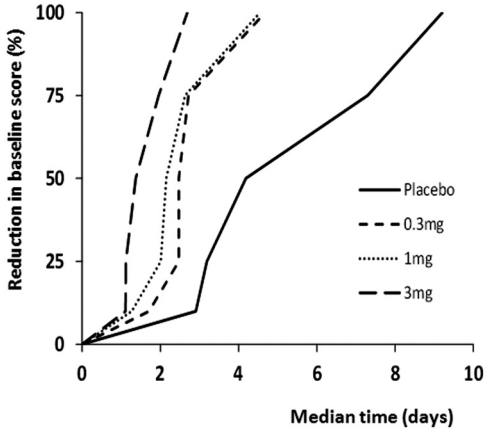

Figure 1. Median time to each level of reduction in the baseline score for the midline ventricles for each drug group.

The modified Graeb scale[9] divided the lateral ventricles into anterior (anterolateral) and posterior halves (posterolateral), the third ventricle into anterior and posterior halves, and the fourth ventricle into superior and inferior halves (Supplemental Figure III). "Ipsilateral" or "contralateral" ventricles were defined relative to catheter-associated rtPA administration, because the impact of IVH and intracerebral hemorrhage laterality has been reported elsewhere.[10] A.J.S.W., S.M., and N.L.U. independently scored CLEAR-IVH safety scans, whereas CLEAR-IVH dose-finding scans were scored by A.J.S.W. and D.F.H. "Stability" CT was the first scan with no catheter-tract hemorrhage or intracerebral hemorrhage growth >5 mL. Interindividual agreement was assessed by κ statistics. Change in total score across all regions compared with the stability CT was correlated with change in IVH volume measured by computer-assisted volumetrics.

Reduction in score to 90%, 75%, 50%, or 25% of the stability CT (t_{90}, t_{75}, t_{50}, t_{25}) was compared between regions and dose by Kaplan-Meier survival analysis (log-rank test). Effect of baseline score, ventricular region, and drug dose was modeled by Cox proportional hazards with and without an interaction term between dose and region. Sensitivity analyses excluded patients who were censored within 7 days or excluded the placebo group.

Results

Patient characteristics have been reported previously.[8] There was high interobserver agreement scoring the 12 ventricular subregions (κ=0.607; 95% CI, 0.59–0.62; P<0.0001) and categorizing each ventricle into quartiles (κ=0.732; 0.70–0.76). Change in baseline score and IVH volume were highly correlated (r^2=0.651, 0.640, and 0.628; P<0.0001).

Median time to reduction in the total score decreased with increasing drug dose (log-rank: t_{90} P=0.001, t_{75} P<0.001, t_{50} P<0.001, t_{25} P=0.003) and was most different for placebo versus 3 mg ($t_{50:}$ placebo—11.43 days, 95% CI, 5.68–17.18; 0.3 mg—3.19 days, 1.00–5.38; 1 mg—3.54 days, 0.45–6.64; 3 mg—2.59 days, 1.72–3.46). With placebo, IVH resolved quickest in the midline ventricles with no difference between anterolateral and posterolateral ventricles. With rtPA, IVH resolution was dose-dependent, quickest in the midline ventricles (Figure 1), next quickest in the anterolateral ventricles, and slowest, with no dose–effect, in the posterolateral ventricles (Table).

rtPA dose and region independently determined t50 (Cox proportional hazards: P<0.0001: dose–effect: per 1 mg rtPA: hazard ratio [HR], 1.47; 1.30–1.67; P<0.0001; location–effect: midline versus anterolateral HR, 1.71; 1.08–2.71; P=0.022; midline versus posterolateral HR, 4.05, 2.46–6.65, P<0.0001; baseline score HR, 0.96, 0.91–1.01, P=0.097; Figure 2) with a greater dose–effect in the midline ventricles (dose–region interaction: P=0.005). Sensitivity analyses showed the same result (excluding 10 censored patients: rtPA: HR, 1.46, 1.29–1.66; versus anterolateral HR, 1.59, 0.98–2.57, versus posterolateral HR, 3.57, 2.14–5.99; excluding placebo: rtPA: HR, 1.27, 1.06–1.65; versus anterolateral HR, 1.16, 0.64–2.08, versus posterolateral HR, 3.70, 2.02–6.85).

Discussion

IVH cleared quickest in the midline ventricles, even with placebo, probably due to a higher turnover of cerebrospinal fluid. This regional difference was greater with rtPA, probably due to greater drug exposure with greater proximity of IVH to the EVD. Once the midline ventricles were open, rtPA is diverted away from the posterolateral ventricles, potentially limiting the effectiveness of intraventricular rtPA in regions distant to the EVD.

This development of the Graeb score[9] assesses ventricular obstruction by region, does not overweight the midline ventricles, is simple to perform, and is strongly correlated with changes in blood volume. However, the dose–effect in the midline ventricles was not seen in another study looking at dose of intraventricular fibrinolysis,[11] although this nonrandomized study only compared 2 doses of rtPA with a

Table. Baseline Characteristics and Median Time to ≤50% of the Baseline Score According to Ventricular Region and Drug Dose

	Dose, mg					
	Placebo (n=22)	0.3 (n=8)	1 (n=8)	3 (n=26)	All (n=64)	Dose *P* Value
Midline	4.96	2.47	2.15	1.37	2.76	<0.001
(n=62)	(3.82–6.11)	(0.42–4.52)	(0.97–3.33)	(0.88–1.87)	(1.79–3.73)	
Anterolateral	9.22	2.72	3.00	2.02	3.40	<0.001
(n=64)	(4.17–14.3)	(1.72–3.72)	(0.00–6.72)	(1.28–2.76)	(2.27–4.53)	
Posterolateral	11.2	2.47	5.23	7.79	8.30	0.199
(n=64)	(7.11–15.3)	(0.00–7.99)	(0.00–27.1)	(1.03–14.6)	(5.44–11.2)	
Region *p*	0.048	0.448	0.009	<0.001	<0.001	

P values are from log-rank tests.

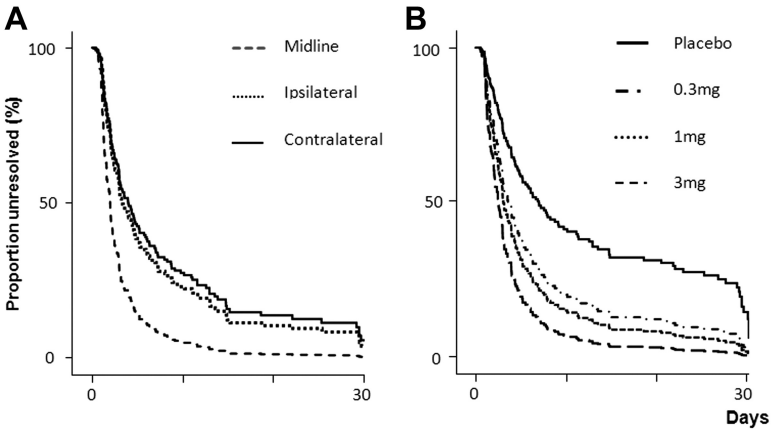

Figure 2. Cox proportional hazard model of time until intraventricular hemorrhage (IVH) score has reduced to ≤50% of the stability CT score with dose, baseline score, and region as independent variables. **A**, Clearance by region. **B**, Clearance by dose group.

poorer temporal resolution of CT scans. This analysis only assessed the regional dose-dependence of IVH clearance because the safety aspects of intraventricular rtPA have already been reported,[8] but it provides a method for analyzing the region-dependent effect of rtPA on clinical outcomes in future trials such as CLEAR III. However, future studies will be needed to address dose–safety and whether distribution or severity of IVH should determine EVD location or rtPA dose.

In conclusion, rtPA administered through an EVD increases resolution of IVH in a dose-dependent fashion and has a greater effect on the midline ventricles and anterolateral sections of the lateral ventricles than the posterolateral ventricles. It is likely to increase the rate of resolution of obstructive hydrocephalus but has a less significant effect on blood in the posterolateral ventricles.

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Disclosures

Johns Hopkins has applied for a use-patent and Genentech has licensed this patent for rtPA use.

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