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Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the CLEAR IVH Program

Alastair JS Webb, BMBCh[*], **Natalie L Ullman, BS**[†], **Sarah Mann, MD**[†], **John Muschelli, ScM**[†], **Issam A Awad, MD**[≠], and **Daniel F Hanley, MD**[†]

Alastair JS Webb: alastair.webb@ndcn.ox.ac.uk; Natalie L Ullman: nullman1@jhmi.edu; Sarah Mann: mannsarah85@googlemail.com; John Muschelli: jmuschel@jhsph.edu; Issam A Awad: iawad@uchicago.edu; Daniel F Hanley: dhanley@jhmi.edu

[*]Department of Clinical Neurosciences, University of Oxford, UK

[†]Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, USA

[≠]Department of Surgery (Neurosurgery), University of Chicago, USA

Abstract

Background and Purpose—The CLEAR-IVH program is assessing the efficacy of intraventricular recombinant tissue 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 12–24 hours of spontaneous IVH were randomized to placebo, 0.3mg, 1mg or 3mg of rtPA twice daily via an extraventricular drain. Twelve subregions of the ventricles were scored from 0–4. Effect of dose on IVH clearance to 50% (t_{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 (t_{50}: log-rank p<0.0001; placebo-11.43 days, 95%CI 5.68–17.18; 0.3mg– 3.19d, 1.00–5.38; 1mg– 3.54d, 0.45–6.64; 3mg– 2.59d, 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 (t_{50}: p<0.0001; rtPA dose: HR=1.47, 1.30–1.67; midline vs anterior-lateral HR=1.71, 1.08–2.71; midline vs posterior-lateral HR=4.05, 2.46–6.65; baseline score HR=0.96, 0.91–1.01), with a significant interaction between dose and ventricular region (p=0.005).

Conclusions—rtPA accelerates resolution of intraventricular hemorrhage. This effect is dose-dependent, is greatest in the midline ventricles and least in the posterior-lateral ventricles.

Clinical Trial Registration—http://www.clinicaltrials.gov: NCT00650858.

Keywords

Intraventricular hemorrhage; Thrombolysis; Randomized controlled trials

Corresponding author: Professor Hanley, Division of Brain Injury Outcomes, Johns Hopkins Medical Institutions, 1550 Orleans Street 3M53-South, Baltimore, MD, USA, Tel: 410-614-6996, Fax: 410-502-7869.

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Introduction

Intraventricular hemorrhage (IVH) complicates 40% of intracerebral hemorrhage (ICH)[1] and increases mortality,[2] due to larger associated ICH and occlusion of the 3rd and 4th ventricles. However, normalization of intracranial pressure does not reverse the neurological deficit,[3] probably because of direct toxicity of blood products.[4] Recombinant tissue plasminogen activator (rtPA) increases resolution of IVH,[5–8] reducing intracranial pressure, duration of CSF diversion and direct neural injury. The clinical efficacy of rtPA is being assessed in the CLEAR-III trial. This analysis of the Safety[8] and Dose-Finding phases of the CLEAR-IVH program assesses the effect of rtPA dose according to ventricular region (supplemental data, http://stroke.ahajournals.org).

Methods

CLEAR-IVH: Safety recruited 48 patients aged 18–75 years old, who had at least one CT scan after insertion of an extra-ventricular drain (EVD) and started treatment within 12–24 hours of a spontaneous IVH.[8] They received 3mg of 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 0.3mg or 1mg rtPA according to the same protocol. The second phase of this study was excluded due to a different dosing schedule.

The modified Graeb scale[9] divided the lateral ventricles into anterior (antero-lateral) and posterior halves (postero-lateral), the third ventricle into anterior and posterior halves and the 4th ventricle into superior and inferior halves (supplemental figure 3, http://stroke.ahajournals.org). 'Ipsilateral' or 'contralateral' ventricles were defined relative to catheter-associated rtPA administration, as the impact of IVH and ICH laterality has been reported elsewhere.[10] AW, SM and NU independently scored CLEAR-IVH: Safety scans, whilst CLEAR-IVH: Dose-Finding scans were scored by AW and DH. 'Stability' CT was the first scan with no catheter-tract hemorrhage or ICH growth >5cc. Inter-individual agreement was assessed by kappa statistics. Change in total score across all regions compared to 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 were 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 inter-observer agreement scoring the twelve ventricular subregions (kappa=0.607, 95% CI 0.59–0.62, p<0.0001) and categorizing each ventricle into quartiles (kappa=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 3mg (t_{50}: placebo- 11.43 days, 95%CI 5.68–17.18; 0.3mg– 3.19d, 1.00–5.38; 1mg– 3.54d, 0.45–6.64; 3mg– 2.59d, 1.72–3.46). With placebo, IVH resolved quickest in the

midline ventricles, with no difference between anterior-lateral and posterior-lateral ventricles. With rtPA, IVH resolution was dose-dependent, quickest in the midline ventricles (figure 1), next quickest in the anterior-lateral ventricles and slowest, with no dose-effect, in the posterior-lateral ventricles (Table 1),

rtPA dose and region independently determined t50 (Cox-Proportional Hazards: p<0.0001: Dose-effect: per 1mg rtPA: HR=1.47, 1.30–1.67, p<0.0001; Location-effect: midline vs anterior-lateral HR=1.71, 1.08–2.71, p=0.022, midline vs posterior-lateral HR=4.05, 2.46–6.65, p<0.0001; baseline score HR=0.96, 0.91–1.01, p=0.097, see 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; vs anterior-lateral HR=1.59, 0.98–2.57, vs posterior-lateral HR=3.57, 2.14–5.99; excluding placebo: rtPA: HR=1.27, 1.06–1.65; vs anterior-lateral HR=1.16, 0.64–2.08, vs posterior-lateral 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 CSF. 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 open, rtPA is diverted away from the posterior-lateral 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, doesn't over-weight 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 non-randomized study only compared two doses of rtPA, with a poorer temporal resolution of CT-scans. This analysis only assessed the regional dose-dependence of IVH clearance as 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 anterior-lateral sections of the lateral ventricles than the posterior-lateral ventricles. It is likely to increase the rate of resolution of obstructive hydrocephalus but has a less significant effect on blood in the posterior-lateral ventricles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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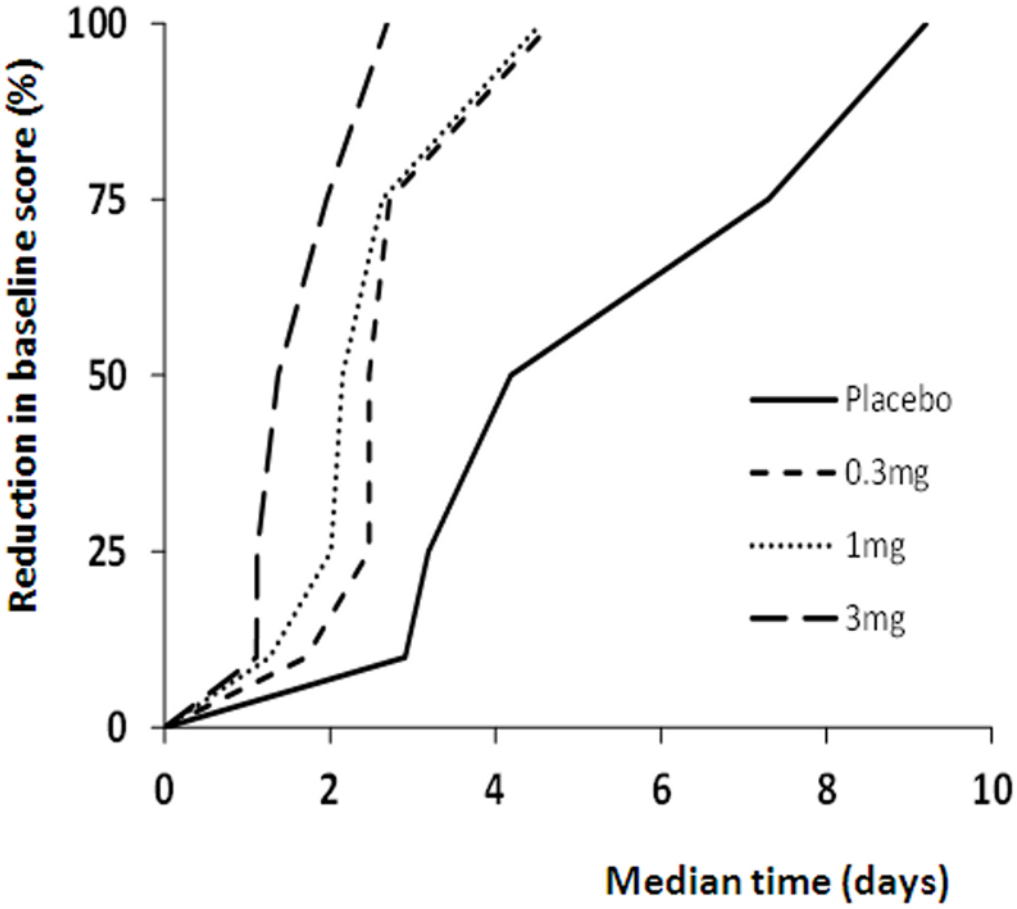

Figure 1.
Median time to each level of reduction in the baseline score for the midline ventricles for each drug group.

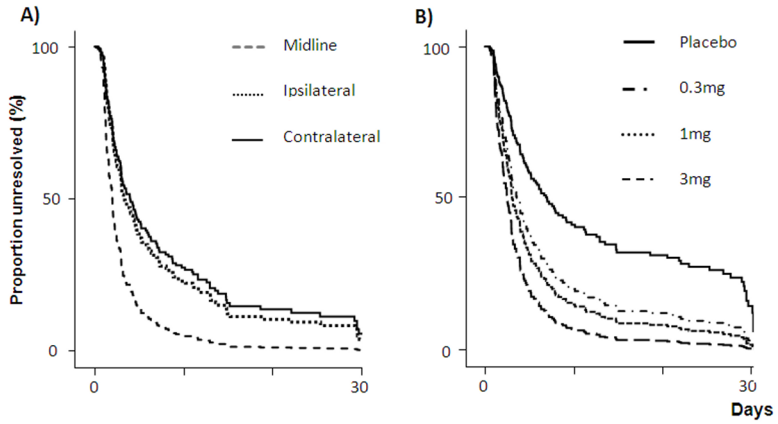

Figure 2.

Cox Proportional-Hazard model of time until IVH score has reduced to ≤50% of the stability CT score, with dose, baseline score and region as independent variables.

Table 1

Baseline characteristics and median time tox ≤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 (n=62)	**4.96** (3.82– 6.11)	**2.47** (0.42– 4.52)	**2.15** (0.97– 3.33)	**1.37** (0.88– 1.87)	**2.76** (1.79– 3.73)	<0.001
Anterior-lateral (n=64)	**9.22** (4.17– 14.3)	**2.72** (1.72– 3.72)	**3.00** (0.00– 6.72)	**2.02** (1.28– 2.76)	**3.40** (2.27– 4.53)	<0.001
Posterior-lateral (n=64)	**11.2** (7.11– 15.3)	**2.47** (0.00– 7.99)	**5.23** (0.00– 27.1)	**7.79** (1.03– 14.6)	**8.30** (5.44– 11.2)	0.199
Region p-value	0.048	0.448	0.009	<0.001	<0.001	

P-values are from log-rank tests.