# Ventricular Catheter Location and the Clearance of Intraventricular Hemorrhage

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## Abstract

**Background**—There is no consensus regarding optimal position of external ventricular drain (EVD) with regard to clearance of intraventricular hemorrhage (IVH).

**Objective**—To assess the hypothesis that EVD laterality may influence the clearance of blood from the ventricular system, with and without administration of thrombolytic agent.

**Methods**—The EVD location was assessed in 100 patients in two CLEAR Phase II trials assessing the safety, and dose optimization of thrombolysis through the EVD to accelerate the clearance of obstructive IVH. Laterality of catheter was correlated with clearance rates.

**Results**—Clearance of IVH over the first 3 days was significantly greater when thrombolytic was administered as compared to placebo, regardless of catheter laterality (p < 0.005, CI −14.0, −4.14 for contralateral EVD and CI −24.7, −5.44 for ipsilateral EVD, respectively). When thrombolytic was administered, there was a trend of more rapid clearance of total IVH through an EVD placed on the side of dominant intraventricular blood as compared to an EVD on the side with lesser blood (P = 0.09; CI −9.62, 0.69). This was not true when placebo was administered. Clearance of 3rd and 4th ventricular blood was unrelated to EVD laterality.

**Conclusion**—It is possible that placement of EVD may be optimized to enhance the clearance of total IVH if lytic agents are used. Catheters on either side can clear the 3rd and 4th ventricles with equal efficiency.

## Keywords

external ventricular drain; intraventricular hemorrhage; thrombolysis

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## Introduction

Intraventricular hemorrhage (IVH) is frequently associated with intracerebral hemorrhage[1], and the volume of associated IVH a significant and independent predictor of mortality and disability in this disease[1–8]. An external ventricular drain (EVD) is commonly used to control intracranial pressure, and to divert cerebrospinal fluid in the setting of hydrocephalus, but also to help clear ventricular blood[11–12]. It is not known whether EVD placement in the lateral ventricle with greater or lesser blood encasement results in greater clearance of IVH, and whether this is different when administering intraventricular thrombolysis. These questions are retrospectively addressed in patients who underwent EVD placement and intraventricular treatment with placebo or recombinant tissue plasminogen activator (rt-PA) in the setting of the recently completed CLEAR IVHPhase II trials, in which results have recently been published[13].

## Patients and Methods

The CLEAR IVHtrials included patients with obstructive $3^{rd}$ or $4^{th}$ ventricular IVH with small associated ICH (< 30 ml on initial eligibility CT scan), excluding patients with known or suspected vascular anomaly, tumor, infratentorial hemorrhagic source, or uncorrected coagulopathy. Mean Glasgow Coma Score on admission of enrolled patients was 8.42 (range 3 to 15), mean volume of IVH at stability was 46.95ml (range 1.53 to 164.8 ml), and mean ICH volume was 9.50 ml at stability (range 0 to 42.5 ml; five cases expanded their ICH to > 30 ml after enrollment). All enrolled patients received EVD placementwith the aim of ICP control. Side of EVD placement was at the discretion of the treating neurosurgeon. The initial safety study (n = 48) used a randomization scheme of 1:1 and the remaining 52 patients were part of the dose-finding tiers, so all patients in those tiers received t-PA at varying doses and intervals. 78 patients ultimately received0.3 to 3 mg of rt-PA doses every 8 to 12 hours, while 22 patientsreceived saline placebo through the EVD at similar volume/ frequency. After each injection of the study agent and a standardized saline flush, the EVD was closed for 1 hour, following which the EVD was reopened to resume ventricular drainage. Drainage criteria (intermittent versus continuous), and particular threshold for drainage were left to the investigators and treating physician's prerogative, as per local practice standards. Thetrial protocolwas approved by the Institutional Review Boards of all participating centers.

Laterality of EVD location was assessed after the conclusion of the trials by review of the CT scan thatwas required after placement of each new EVD catheter, including bone windows to better visualize catheter perforations. Review was conducted by two investigators (JJ and IAA) blinded to treatment status, IVH volume clearance data, or other clinical information. Categorization of EVD laterality was determined by consensus among the two investigators according to prospectively articulated criteria, as ipsilateral (catheter perforations are in the lateral ventricle with greater IVH distribution, with or without extension of some perforations into the third ventricle), contralateral (catheter perforations are in the lateral ventricle with lesser IVH distribution, with or without extension of some perforations into the third ventricle), or other (including cases with bilateral symmetric IVH, catheter perforations crossing into both lateral ventricles, or cases who underwent placement of dual or bilateral catheters in the first three days).

Prospective, protocolized imagingallowed assessment of total IVH volume on daily computed tomographic (CT) scansin all cases, blinded to the treatment assignment. In addition, volume of $3^{rd}$ and $4^{th}$ ventricular blood was prospectively assessed in cases receiving thrombolytic (as part of dose escalation pharmacokinetics study). The volumetric assessmentswere calculated by the trial's Imaging Center staff using free-hand tracing with

medical imaging software (Alice®, Perceptive Informatics - Boston, Massachusetts), and methods similar to those reported in other studies[14]. Clearance rates of IVH were determined using daily IVH volume, relative to initial IVH volume (defined on stability CT scan approximately 6 hours after EVD placement). Population-averaged models were fit for each cohort, and predictors and their interactions includedtime course of clearance and the variables of treatment status (thrombolysis or placebo) and EVD location (ipsilateral or contralateral to dominant IVH). The two variables of treatment status and catheter laterality were assumed to be independent of each other. These models were fit using generalized estimating equations (GEE), with exchangeable correlation, robust standard error, no intercept, and an offset of 100. The offset was used since each clearance is assumed to be 100% at stability (time 0) [15]. Beta coefficients represented the average clearance rates (slopes) for each group, and these were plotted for 3 days after IVH stability, and compared using Wald t-tests, with confidence intervals and significance. The 3-day analysis was chosen because all patients had EVDs in place during this time and were receiving active treatment and daily neuroimaging unless death occurred. EVD laterality was determined by the presence of catheter perforations in the respective lateral ventricle.

## Results

Figure 1 illustrates the distribution ofEVD placements in relation to dominant lateral ventricle IVH, and examples of typical ipsilateral and contralateral placements. There was no significant difference in CSF volume drained during the index period among cohorts with ipsilateral versus contralateral catheter locations (mean: 128ml versus 165 ml, respectively; p = 0.139). Nine of 66 (14%) cases with initial contralateral EVDplacement, and 1 of 15 (6%) cases with initial ipsilateral placement resulted in clogging or malfunction of EVD or decision to place a second catheter in the contralateral ventricle (difference not statistically significant, p = 0.679). There were no significant differences between the ipsilateral and contralateral groups in terms of gender, age, baseline Glasgow Coma Score, initial IVH volume, initial ICH volume, or in the CSF drained during the 3-day index period of drainage (Table 1). The mean total rt-PA dose administered during the 3-day index period of drainage was significantly larger in the cases with EVD contralateral to dominant IVH as compared to ipsilateral cases (11.8 mg and 5.21 mg, respectively, p = 0.02).

For clearance comparisons, we limited our analysis to the 81 cases where EVD was clearly ipsilateral or contralateral to the dominant lateral ventricle clot during the index period of drainage. We hence excluded cases where the catheter crossed into both lateral ventricles (n = 11), where EVD catheter was changed to the opposite side (n = 10), and cases with more than a single catheter during the 3-day index period of drainage (n = 8) (Tables 2 and 3). Figure 2 illustrates best-fit total IVH clearance rates, in cohorts receiving placebo or rt-PA through the EVD. There was significantly greater total IVH clearance in rt-PA-treated compared to placebo patients for both contralateral (P < 0.001; CI −14.01, −4.14) and ipsilateral (p = 0.002; CI −24.7, −5.44) placements, respectively. There was a trend of more rapid total IVH clearance in ipsilateral versus contralateral placement in the rt-PA cohort, which did not reach statistical significance (P = 0.09; CI −9.62, 0.69). This trend was not observed in the in placebo patients. Figure 3 illustrates best-fit clearance rates of 3rd and 4th ventricular IVH, with no significant difference with ipsilateral and contralateral EVD locations.

## Discussion

Cases enrolled in theCLEAR IVH trials achieved more rapid clearance of IVH and improved outcome in rt-PA treated cases[13]. Dose optimization, safety profile, and estimates of outcome have motivated a recently launched Phase III trial for more definitive assessment

of the potential benefits of thrombolysis[16]. However, there is no consensus in these trials or in current neurosurgical practice about optimal EVD placement laterality to enhance IVH clearance.

Our analysis suggests that cases with EVD placement ipsilateral to dominant IVH may exhibit a trend toward more rapidtotal clearance of IVHover the first 3 days when receiving thrombolysis, likely related to the access of rt-PA to the dominant ventricular clot. While this trend did not reach statistical significance, it was noted despite a significantly lower rt-PA dose administered in the ipsilateral cases. Such trend toward different clearance ratesbetween ipsilateral and contralateral groups was not noted in the placebo cases, possibly because of obstruction by recalcitrant clot when EVD is placed in the dominant lateral ventricular clot. Third and fourth ventricular blood cleared at equal rates with EVD locations ipsilateral and contralateral to dominant IVH distribution.

Limitations of these data relate to the non-random assignment of catheter placement, with neurosurgeons more typically choosing the less involved ventricle a priori, but without definite consensus on this choice. This was not an intention-to-treat analysis, as there was never an articulated intention about laterality. Comparisons were limited to the cohorts with EVD locationsthatwere clearly ipsilateral or contralateral to the dominant IVH during the 3-day index period of clearance. And two cohorts were comparable in terms of ICH volume, IVH volume, age, sex and initial GCS. The rate of catheter obstructions leading to switching laterality from ipsilateral to contralateral and vice versa was not significantly different. Cases where catheters crossed into both lateral ventricles and cases where laterality of catheter placement was changed during the period of drainage were excluded from analysis. We also excluded cases that required bilateral catheters at any time during the 3-day index period of drainage. Such cases requiring bilateral catheters were more likely associated with larger casted IVH, hence introducing greater bias if they were included in this analysis. The numbers of cases in each variable stratum were too small to allow comprehensive multivariate modeling of clearance rates in relation to catheter placement.

The cases included varying doses of rt-PA as part of dose optimization in Phase II study, and all thrombolysis cases were analyzed as a group, in comparison to placebo cases. There were too few cases in each dose stratum to allow a comparison of impact of catheter laterality at lower versus higher rt-PA doses. The lack of multivariate analysis is acknowledged as an important limitation of the study. But in fact the total dose of rt-PA used during the index period of drainage was greater in contralateral than ipsilateral EVD groups. This difference may reflect an imbalance in randomization in different dose strata, or possibly a dependant outcome, due to stopping rt-PA dose earlier in the ipsilateral group because of more rapid IVH clearance. Regardless, this would not be expected to introduce a bias in favor of greater clearance of IVH in the ipsilateral group, and would not account for the observed trend toward more rapid clearance in theipsilateral group.

Various practice patterns including drainage thresholds were allowed that may have affected IVH clearance, but we have no reason to suspect that these were applied differently of ipsilateral versus contralateral EVD cases. In fact, we present data on CSF drainage, indicating no significant difference between the cohorts during the index period of drainage. This is the best available information to date regarding impact of EVD lateralityon IVH clearance, with randomization of thrombolysis versus placebo, and adjudicated assessment of IVH clearance. Finally, it is possible that any differences of IVH clearance rates could equalize after the acute period, so this information is noted to apply to acute IVH clearance, as defined, in the first three days. The possible impact of EVD localization on ICP control and outcome are beyond the scope of this report. These and analysis of the cohort of CLEAR cases with dual catheters are planned in another communication. And we certainly

cannot correlate clearance rates with clinical benefit, although this hypothesis is being addressed in the ongoing CLEAR III trial.

The currently favored practice of placing initial EVD contralateral to the dominant lateral ventricular IVH would still seem to be justified. Other analysis of intracranial pressure control also appears to favor this location (Ziai W, et al. manuscript in preparation). We also provide evidence of equal effectiveness of ipsilateral and contralateral catheter locations in clearing third and fourth ventricular blood, often the main cause of obstructive hydrocephalus. Hence, the placement of initial EVD contralateral to dominant lateral ventricle IVH remains the recommended strategy in the ongoing CLEAR Phase III trial protocol, since the primary aim of EVD placement is control of intracranial pressure and relief of hydrocephalus, andhalf the patients in that trial will be randomized to receive placebo, and the investigator would not know if rt-PA is being administered. But in clinical practice where thrombolysis may be planned in exceptional or compassionate use outside the scope of a trial, or in ineligible cases for the trial, it is possible that an EVD location ipsilateral to dominant IVH may enhance total IVH clearance, with greater access of thrombolytic agent to the recalcitrant clot cast. This hypothesis is illustrated in a case example from the trial, showing prompt clearance with thrombolysis through ipsilateral EVD in the casted ventricle (Figure 4). Similarly, it is possible that a second catheter might be justified in the casted ventricle to help enhance the benefits of thrombolysis, if the initial EVD was placed in contralateral location. This is illustrated in a second case example, where thrombolytic agent in contralateral EVD resulted in slow clearance of major casted blood in the opposite ventricle during the index period, and a subsequent second catheter was placed in the dominant clot, resulting in prompt clearance (Figure 5). This was also suggested in a recent report of greater IVH clearance with dual catheters, compared to volume matched IVH cases treated with a single catheter[17].

It may be possible to optimize the placement of EVD to enhance the clearance of total IVH if lytic agents are used. Catheters on either side can clear the 3d and 4th ventricles with equal efficiency. Further research, with a larger sample size, is required to make definitive conclusions concerning ipsilateral vs. contralateral EVD placement.

## Acknowledgments

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## Catheter Placement Distribution in Relation to Dominant Side for Ventricular Blood

N = 11, (11%)

N = 8, (8%)

N = 15, (15%)

N = 66, (66%)

| | Contra | | Ipsi |
|---|---|---|---|
| | Dual Catheters | | Bilateral* |
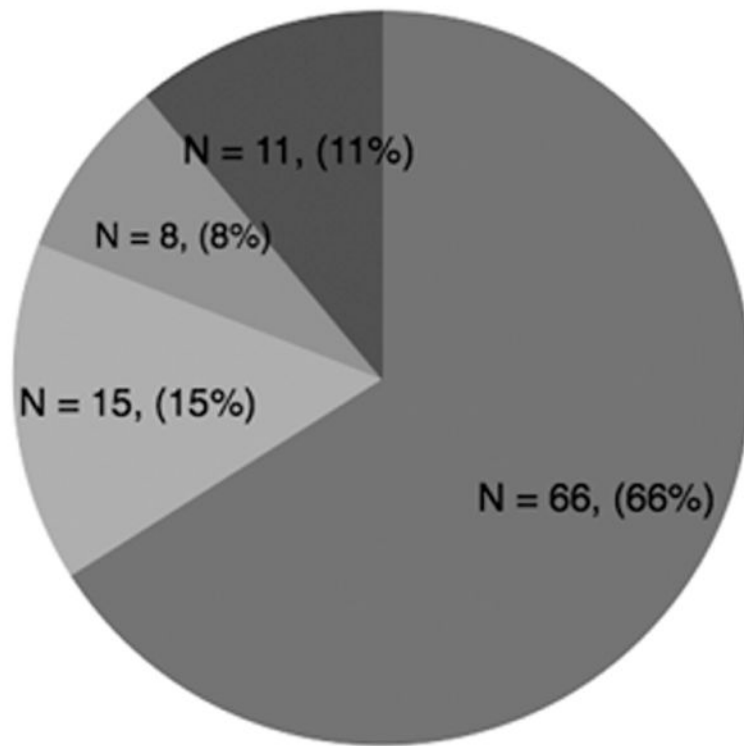
*Bilateral denotes EVD catheter traversing both lateral ventricles, or IVH involving both lateral cerebral ventricles equally
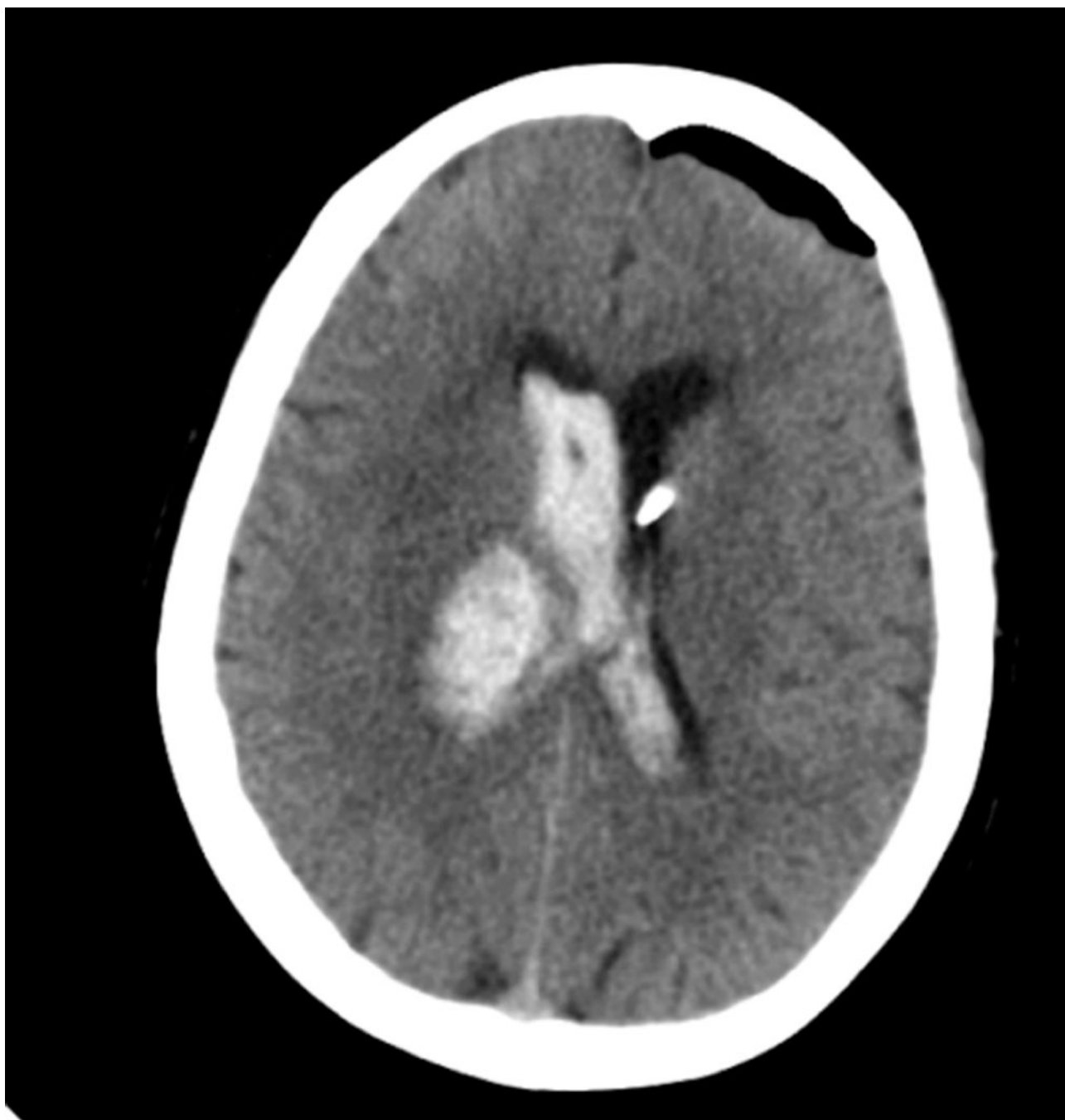
**Figure 1.**
Distribution of initial catheter placements for CLEAR Phase II enrolled subjects (A). CT scan of typical ipsilateral (B) or contralateral (C) EVD placement.
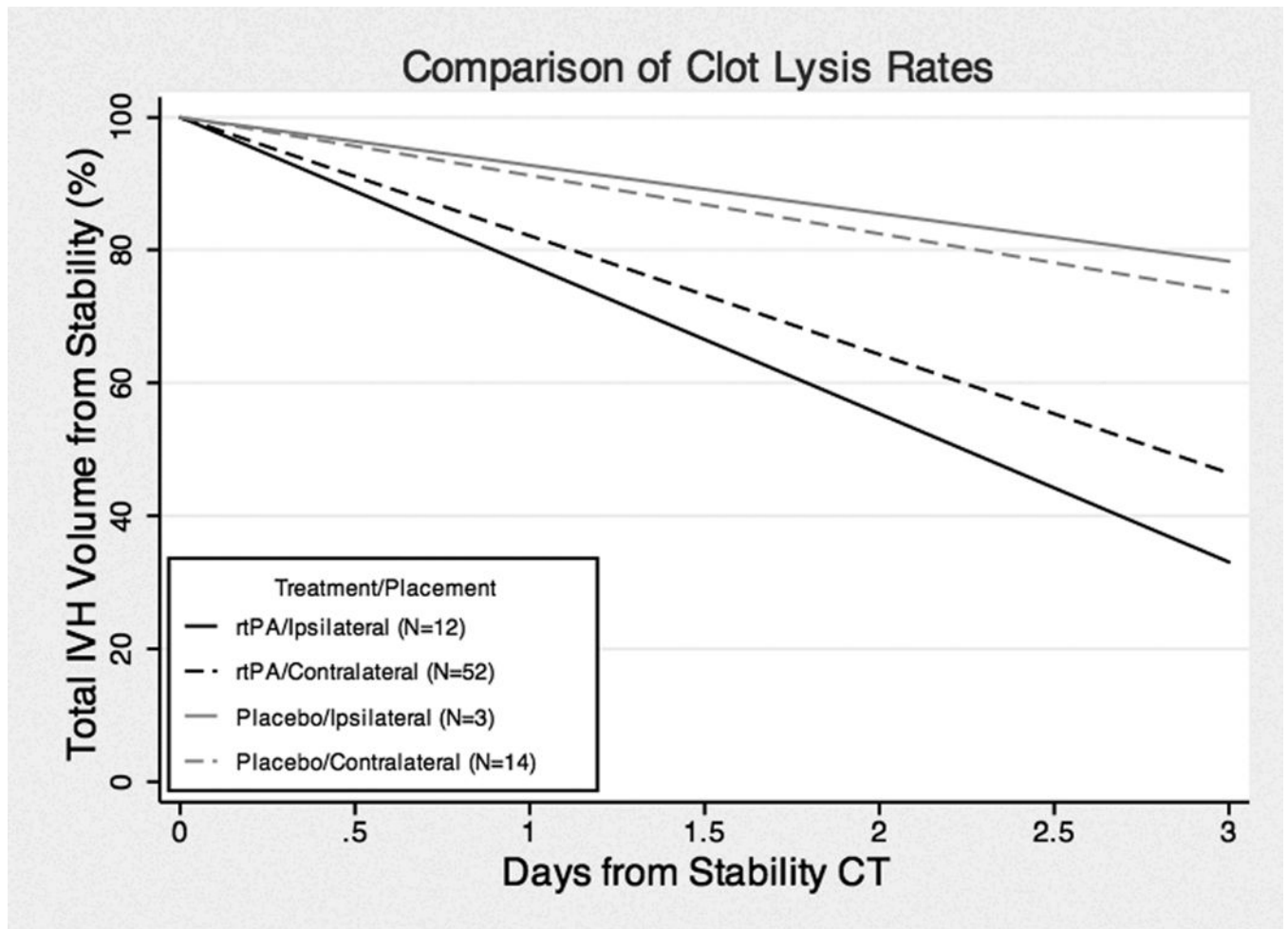
**Figure 2.**
Best fit curves of total IVH clearance rates among ipsilateral and contralateralcatheter placement cohorts, with placebo or thrombolytic, from 100% volume at stability.
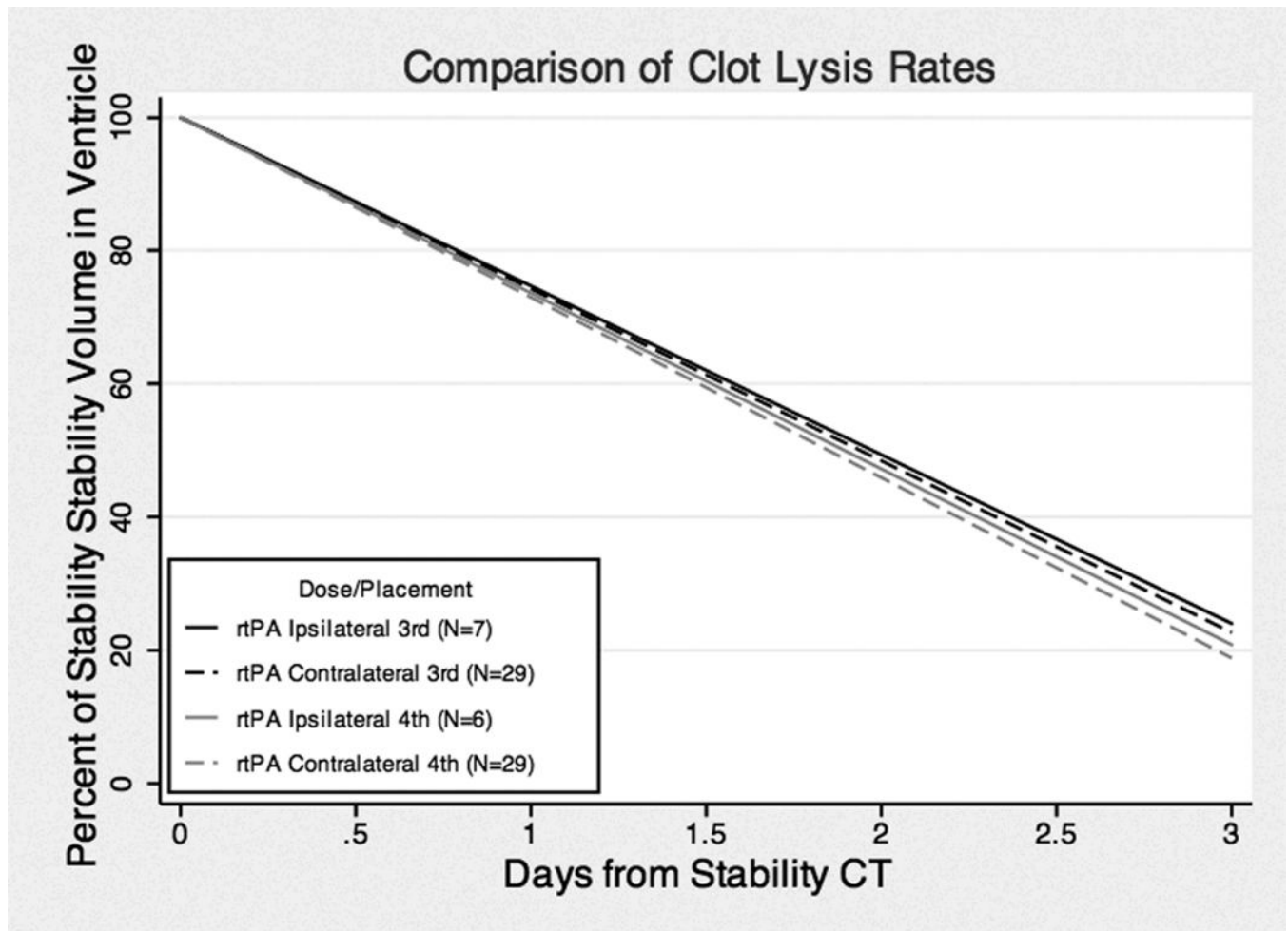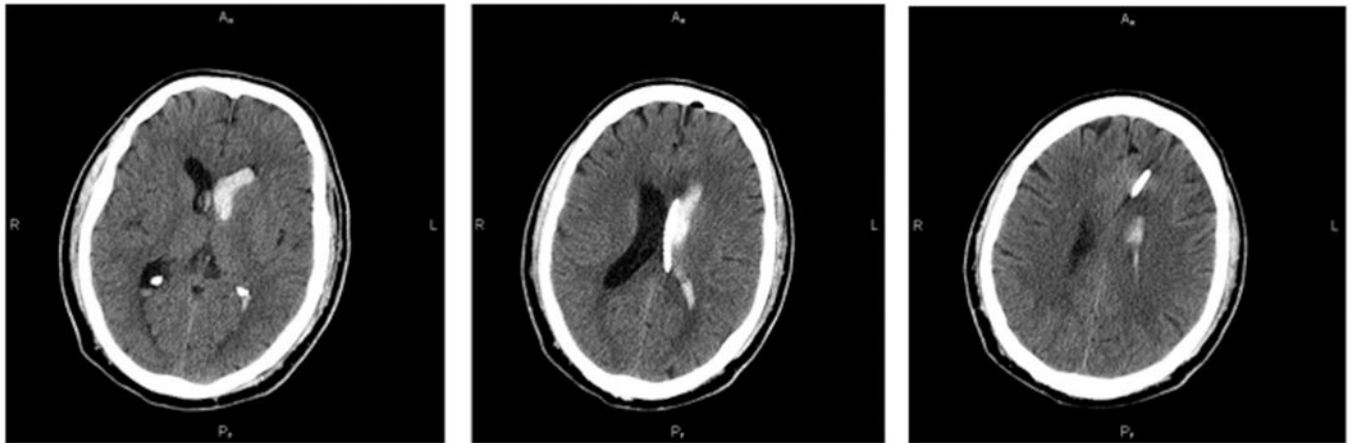
**Figure 3.**
Best fit curves of 3rd and 4th ventricular clearance rates among ipsilateral and contralateral catheter placement cohorts with thrombolytic from 100% volume at stability.

# Ipsilateral EVD Placement
# Confined to the Body of the Lateral Ventricle
# with Casted IVH



# Favorable Clearance After a Single Dose of
# rTPA Through Ipsilateral EVD in Dominant
# Lateral Ventricular Cast

**Figure 4.**
Illustrative case, where EVD was placed ipsilateral to dominant lateral ventricular IVH, with catheter deflected by the septum pellucidum and achieving maximal longitudinal contact

with the intraventricular blood cast (A). Excellent clearance of IVH was accomplished after a single dose of rt-PA (B).

# Ineffective IVH Clearance
# by Contralateral EVD

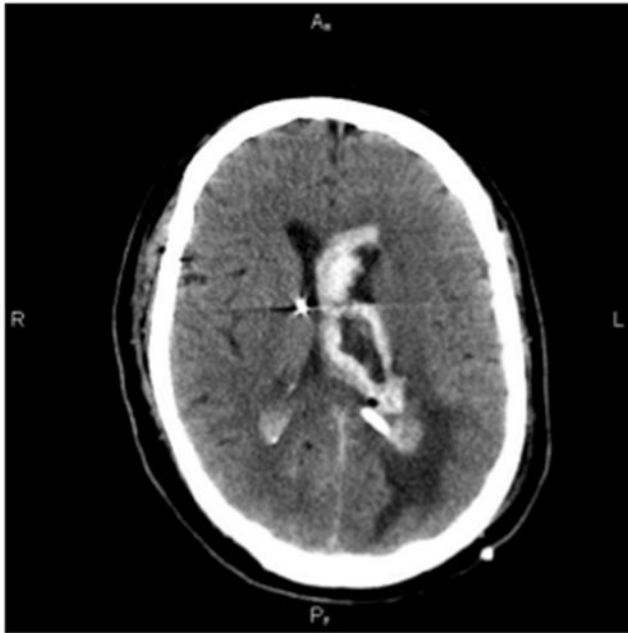**Initial contralateral EVD placement**

**Minimal clearance of contralateral casted lateral ventricle after 3 doses of rTPA, 48 hours**

# Salvaged Clearance of Casted Trapped Ventricle by Ipsilateral Catheter

## Ipsilateral EVD placement, favorable clearance after one rTPA dose

## Complete ventricular clearance after 9 total doses



**Figure 5.**
Illustrative case, where initial EVD was placed contralateral to dominant IVH, and poor clearance of the blood was noted in the trapped lateral ventricle, despite multiple doses of thrombolytic over 48 hours (A). With patient in poor neurologic condition, presumed from ventricular trapping by casted blood, a second EVD was placed using a posterior approach, into the lateral ventricular blood cast, and this accomplished prompt clearance of the residual IVH, relief of the trapping and shift, and improved neurologic condition (B).

**Table 1**

Baseline Characteristics in Cohorts with Ipsilateral and Contralateral EVD Placements

| | Contralateral | Ipsilateral | P-value |
|---|---|---|---|
| **Gender (M/F)** | 37/29 | 12/3 | 0.09 |
| **Mean Age (years)** | 55.09 | 55.67 | 0.84 |
| **Mean IVH Volume at Stability (mL)** | 44.51 | 37.36 | 0.29 |
| **Mean ICH Volume at Stability (mL)** | 10.76 | 8.25 | 0.35 |
| **Mean Baseline GCS** | 8.4 | 9.6 | 0.18 |
| **Mean CSF drainage (mL)** [*] | 165.5 | 128.8 | 0.14 |
| **Mean total rt-PA dose (mG)** *in patients receiving rt-PA*[*] | 11.78 | 5.21 | 0.02 |

[*] During the 3-day index period of drainage

**Table 2**

Total IVH Clearance Rates in Ipsilateral and Contralateral EVD Placements Comparing Thrombolytic to Placebo

| Catheter Laterality and Treatment Cohorts | Total IVH Clearance | Significant P Value | Confidence Interval |
|---|---|---|---|
| Thrombolytic Ipsilateral (n = 12) | -22.32 | < 0.001 | (-27.12, -17.52) |
| Thrombolytic Contralateral (n = 52) | -17.89 | < 0.001 | (-19.74, -15.98) |
| Placebo Ipsilateral (n = 3) | -7.24 | 0.089 | (-15.6, 1.12) |
| Placebo Contralateral (n = 14) | -8.78 | < 0.001 | (-13.35, -4.22) |

| Total IVH Clearance in Thrombolytic versus Placebo | | | |
|---|---|---|---|
| Ipsilateral Thrombolytic versus Placebo (n = 15) | -15.08 | 0.002 | (-24.72, -5.44) |
| Contralateral Thrombolytic versus Placebo (n = 66) | -9.07 | < 0.001 | (-14.01, -4.14) |

| Total IVH Clearance in Ipsilateral versus Contralateral EVD Location | | | |
|---|---|---|---|
| Ipsilateral versus Contralateral Thrombolytic (n = 64) | -4.47 | 0.09 | (-9.62, 0.69) |
| Ipsilateral versus Contralateral Placebo (n = 17) | 1.54 | 0.751 | (-11.06, 7.99) |

**Table 3**

3rd and 4th ventricle clearance rates comparing ipsilateral and contralateral EVD placements among cases receiving thrombolytic

| Catheter Laterality Cohorts | 3rd and 4th Ventricular Clearance | Significant P Value | Confidence Interval |
|---|---|---|---|
| **Clearance in 3rd Ventricle Among Ipsilateral and Contralateral EVD Placements** | | | |
| Ipsilateral 3rd Ventricle (n = 8) | −27.22 | < 0.001 | (−34, −20.44) |
| Contralateral 3rd Ventricle (n = 28) | −27.36 | < 0.001 | (−33.72, −20.99) |

| Clearance in 4th Ventricle Among Ipsilateral and Contralateral EVD Placements | | | |
|---|---|---|---|
| Ipsilateral 4th Ventricle (n = 7) | −31.08 | < 0.001 | (−35.4, −26.77) |
| Contralateral 4th Ventricle (n = 28) | −31.35 | < 0.001 | (−33.9, −28.79) |

| 3rd and 4th Ventricle Clearance Among Ipsilateral versus Contralateral EVD Placements | | | |
|---|---|---|---|
| 3rd Ventricle Contralateral versus Ipsilateral (n = 36) | 0.14 | 0.98 | (−9.16, 9.44) |
| 4th Ventricle Contralateral versus Ipsilateral (n = 35) | 0.27 | 0.92 | (−4.75, 5.28) |