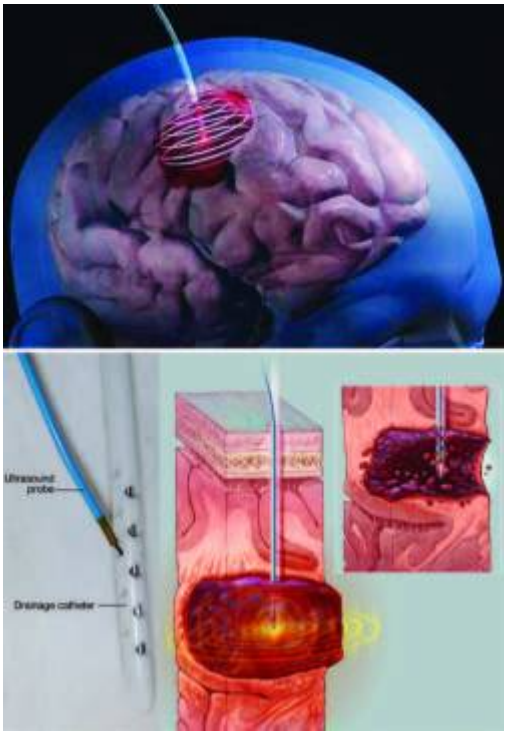
Intraventricular tissue plasminogen activator



- Comparative efficacy of urokinase and recombinant tissue-type plasminogen activators in intraventricular hemorrhage
- Rapidity of hematoma resolution after fibrinolytic therapy for intracerebral hemorrhage has a favorable effect on functional outcome
- Risk of intracerebral haemorrhage with tenecteplase versus alteplase in acute ischaemic stroke: a meta-analysis
- Analysis of Thrombolytic Agents in Intraventricular Hemorrhage: A Systematic Review and Meta-Analysis
- Does stereotactic thrombolysis with alteplase for intracerebral haemorrhage alter intraventricular haematoma volume? A secondary analysis of the MISTIE-III trial
- Tissue Plasminogen Activator in Acute Cardiac Arrest
- Mechanistic Evaluation of Diffusion Weighted Hyperintense Lesions After Large Spontaneous Intracerebral Hemorrhage: A Subgroup Analysis of MISTIE III
- HummingFlow: novel single twist-drill access for ventricular drainage, irrigation, monitoring, and automated local drug delivery in subarachnoid hemorrhage

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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 CLEAR III clinical 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).

✖ In cases of a suspected aneurysm, AVM, or other vascular malformation, it cannot be used until the source of bleeding has been neutralized [2] [3].

℞: 2–5 mg of tPA [4] [5] [6] in NS is administered through an intraventricular catheter (IVC) every 8 hours

for up to 4 days. The IVC is closed for 2 hours after injection [7].

In the low dose CLEAR-IVH (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage) trial (a phase II trial with 52 patients), 1 mg tPA intrathecally via a ventricular catheter every 8 hours up to a maximum of 4 days, was associated with a 30 d mortality of 15% (compared to an expected 80–85%) [8] The hemorrhagic complication rate was 6%.

Luong et al. evaluated the impact of IVF on the risk of death and the functional outcomes in IVH patients with AOH.

This prospective cohort study included IVH patients with hypertensive intracranial hemorrhage complicated by AOH who required EVD. Luong et al. evaluated the risk of death and the functional outcomes at 1 and 3 months, with a specific focus on the impact of combined EVD with IVF by low-dose rtPA.

Between November 30, 2011 and December 30, 2014, 80 patients were included. Forty-five patients were treated with EVD alone (EVD group) and 35 received IVF (EVD+IVF group). The 30- and 90-day mortality rates were lower in the EVD+IVF group than in the EVD group (42.2 vs. 11.4%, $p = 0.003$, and 62.2 vs. 20%, $p < 0.001$, respectively). The Graeb scores were significantly lower in the EVD+IVF group than in the EVD group ($p \leq 0.001$) during the first 3 days and on day 7 after assignment. The 30-day good functional outcome (modified Rankin Scale [mRS] score 0-3) was also higher in the EVD+IVF group than in the EVD group (6.7 vs. 28.6%, $p = 0.008$). However, the 90-day good functional outcome (mRS score 0-3) did not significantly increase in the EVD+IVF group (30.8% in the EVD group vs. 51.6% in the EVD+IVF group, $p = 0.112$).

In this prospective observational study, EVD+IVF was associated with a lower risk of death in IVH patients. EVD+IVF improved the chance of having a good functional outcome at 1 month; however, this result was no longer observed at 3 months [9].

Adult patients with primary diagnosis of nontraumatic intracerebral hemorrhage requiring ventriculostomy from the Nationwide Inpatient Sample from 2002 to 2011, compared demographics and hospital characteristics, comorbidity, inpatient outcomes, and resource utilization measures between patients treated with IVT and those managed with ventriculostomy, but without IVT. Population estimates were extrapolated using standard Nationwide Inpatient Sample weighting algorithms.

34044 patients in the analysis, of whom 1133 (3.3%) received IVT. The thrombolysis group had significantly lower inpatient mortality (32.4% versus 41.6%; P=0.001) and it remained lower after controlling for baseline characteristics, hospital characteristics, comorbidity, case severity, and withdrawal of care status (adjusted odds ratio, 0.670; 95% confidence interval, 0.520-0.865; P=0.002). There was a trend toward favorable discharge (home or rehabilitation) among the thrombolysis cohort (adjusted odds ratio, 1.335; 95% confidence interval, 0.983-1.812; P=0.064). The adjusted rates of bacterial meningitis and ventricular shunt placement were similar between groups. The thrombolysis group had longer length of stay and higher inflation-adjusted cost of care, but cost

of care per day length of stay was similar to the non-IVT group.

IVT for intracerebral hemorrhage requiring ventriculostomy resulted in lower inpatient mortality and a trend toward favorable discharge outcome with similar rates of inpatient complications compared with the non-IVT group [10].

Urokinase (uPA) and tissue plasminogen activator (tPA) are used for IVF in Human. No clinical trial has evaluated the differential impact of these two fibrinolytics for IVF.

Although both uPA and tPA led to reduced ventricular volumes, only uPA significantly improved functional recovery. These results could be explained by the fact that uPA, in contrast of tPA, fails to promote inflammatory processes and neurotoxicity [11].

Intraventricular fibrinolysis (IVF) in subarachnoid hemorrhage (SAH) is an emerging strategy aiming to hasten clot lysis, treat hydrocephalus, and reduce permanent shunt rates. Because of clinical heterogeneity of investigated patient effects of IVF on permanent shunt incidence and functional outcome are widely debated. The present study is the first to investigate solely endovascular-treated SAH patients.

88 consecutive patients with aneurysmal SAH requiring external ventricular drain placement and endovascular aneurysm closure were included. Functional outcome and shunt dependency were assessed 90 days after event. A matched controlled sub-analysis was carried out to investigate the effects of IVF treatment (n = 14; matching criteria: age, neuro-status and imaging). Multivariate modeling was performed to identify independent predictors for permanent shunt dependency.

In IVF-patients neurological status was significantly poorer [Hunt&Hess: IVF = 4(3-5) vs. non-IVF = 3(1-5); p = 0.035] and the extent of ventricular hemorrhage was increased [Graeb Score: IVF = 7(6-8) vs. non-IVF = 3(1-4); p ≤ 0.001]. Consecutive matched controlled sub-analysis revealed no significant therapeutic effect of IVF with respect to shunt dependency rate and functional outcome. Multivariate analysis revealed Graeb score [OR = 1.34(1.02-1.76); p = 0.035] and sepsis [OR = 11.23(2.28-55.27); p = 0.003] as independent predictors for shunt dependency, whereas IVF did not exert significant effects (p = 0.820).

In endovascular-treated SAH patients IVF neither reduced permanent shunt dependency nor influenced functional outcome. Despite established effects on intraventricular clot resolution IVF appears less powerful in SAH as compared to ICH. Given the reported positive effects of lumbar drainage (LD) in SAH, a prospective analysis of a combined treatment approach of IVF and subsequent lumbar drain seems warranted aiming to reduce permanent shunting and improve functional outcome [12].

Case reports

A 15-year-old male patient presented after a motor vehicle accident with bilateral extensor posturing, intracerebral and IVH, and acute obstructive hydrocephalus.

A right EVD was placed and functioned only transiently. A left EVD was placed and functioned only transiently. Because of the inability to maintain ventricular drainage, rising intracranial pressure, and worsening clinical status, 5 mg of recombinant-tissue plasminogen activator was injected through

each EVD. Excellent EVD function was obtained quickly, with control of intracranial pressure and improvement in clinical status and without hemorrhagic complication.

With obstructive hydrocephalus secondary to acute traumatic IVH that cannot be controlled with EVD because of recurrent obstruction from intraventricular blood, intraventricular recombinant-tissue plasminogen activator can be effective and safe, despite preexisting multiple hemorrhagic intracranial injuries [13].

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