Safety of Intraventricular rt-PA for Pan-Ventricular IVH Caused by a Ruptured AVM: A Case Report

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Abstract

Intraventricular recombinant tissue plasminogen activator (IVT rt-PA) has improved outcomes for intraventricular hemorrhage (IVH). Patients with suspected or untreated arteriovenous malformations (AVMs) have been excluded from clinical trials. We present a patient with IVH secondary to a ruptured AVM safely treated with IVT rt-PA. A 48-year-old Hispanic male with a history of dermatomyositis presented to the emergency department with sudden left-sided weakness. En route to computed tomography (CT), he became lethargic. Computed tomography revealed extensive IVH with acute hydrocephalus, which was treated with the placement of external ventricular drain with clinical improvement. Computed tomography angiogram performed did not reveal AVM. Cerebral digital subtraction angiogram (DSA) was planned due to suspicion of AVM. Prior to DSA, patient became acutely lethargic. Computed tomography imaging revealed worsening hydrocephalus. External ventricular drain was noted to be draining. Repeat CT revealed improved hydrocephalus but with left lateral ventricle dilatation. Risks and benefits of IVT rt-PA were discussed with the family and a decision was made to treat. Three doses of 1 mg IVT rt-PA were administered with resolution of midline blood and lateral ventricular dilatation with clinical improvement. Digital subtraction angiogram revealed early draining vein on right internal carotid artery injection draining into the inferior sagittal sinus representing ruptured AVM without clear nidus. Repeat DSA with possible embolization was planned after discharge. In spite of additional in-hospital complications, the patient gradually improved and was ultimately discharged home. Our case supports the idea that the use of IVT rt-PA following an IVH caused by an underlying AVM could be further explored in carefully designed clinical trials.

Keywords

intracranial arteriovenous malformations, neurohospitalist, safety, neurocritical care

Introduction

Intraventricular recombinant tissue plasminogen activator (IVT rt-PA) has improved outcomes for patients with intraventricular hemorrhage (IVH). Patients with suspected or untreated arteriovenous malformations (AVMs) have been excluded from trials.¹ We present a patient with IVH secondary to a ruptured AVM safely treated with IVT rt-PA.

initial neuroimaging, the patient was noted to have an acute decompensation, with GCS of 9 (E3V1M5), precipitating a need for intubation.

Brain computed tomography (CT) revealed a right thalamic intraparenchymal hemorrhage with extensive IVH and acute hydrocephalus (Figure 1A). Computed tomography angiography (CTA) did not reveal a vascular malformation. Patient underwent external ventricular drain (EVD) placement on

Case Report

A 48-year-old Hispanic male with a history of dermatomyositis presented to the emergency department with abrupt onset left-sided weakness, noted after experiencing a sudden fall at home. Patient's Glasgow Coma Scale (GCS) on arrival was 14 (E4V4M6), as patient was noted to be confused. During

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Figure 1. Serial CT brain without contrast images. A, Initial CT reveals R thalamic intracerebral hemorrhage with intraventricular extension extending into all 4 ventricles; IVHS 20. B, Repeat CT obtained on hospital day 2 as GCS worsened. Note insertion of EVD, terminating in the third ventricle, and development of mild hydrocephalus; IVHS 23. C, Repeat CT obtained on hospital day 8 at the initiation of IVT rt-PA; IVHS 11. D, Repeat CT obtained on hospital day 10 after completion of 3 doses of IVT rt-PA; IVHS 7. CT indicates computed tomography; GCS, Glasgow Coma Scale; IVHS, Intraventricular Hemorrhage Score; IVT rt-PA, intraventricular recombinant tissue plasminogen activator.

the date of admission, with a subsequent improvement in clinical examination. By the following morning, patient's GCS had improved to 15, and patient was successfully extubated. A cerebral digital subtraction angiogram (DSA) was planned due to suspicion of an underlying vascular malformation. On hospital day 7, before DSA could be obtained, the patient developed significant nausea and emesis and had an acute change in mental status, with GCS decreasing to 13 (E4V4M5). Brain CT revealed worsening hydrocephalus (Figure 1B). External ventricular drain was noted to be draining and its position was lowered. Overnight, EVD drained well with no neurological improvement. Repeat CT revealed improved hydrocephalus, but left lateral ventricle dilatation remained, likely secondary to obstruction of the foramen of Monro (Figure 1C).

Given the persistence of hemorrhagic products, IVT rt-PA was considered as rescue therapy. A left-sided EVD placement was considered, but not performed, due to a presumed high risk of EVD occlusion. Risks and benefits of IVT rt-PA were discussed with the patient's family and a decision was made to treat per CLEAR-IVH protocol. Beginning on hospital day 8, IVT rt-PA was administered at 1 mg every 8 hours for a total of 3 doses and EVD was left open to drain. Repeat imaging revealed resolution of midline blood and lateral ventricular dilatation (Figure 1D). The patient's mental status improved, and he resumed the ability to consistently follow commands.

Digital subtraction angiogram was obtained on hospital day 14, and during right internal carotid artery injection, there was discovery of an early draining vein around a right middle

Figure 2. Digital subtraction angiography showing a right internal carotid artery injection. Antero-posterior (left) and lateral (right) views with early draining vein (arrow).

cerebral artery branch that further drained into the inferior sagittal sinus (Figure 2). This finding was thought to be a ruptured AVM without a clear nidus. The remainder of the patient's hospital course was unremarkable, and his clinical examination remained stable. External ventricular drain was removed, and the patient was ultimately discharged home. A repeat DSA was planned after discharge, but the patient returned to his home country and was lost to follow-up.

Discussion

Intraventricular hemorrhage in adults is caused by a variety of conditions, including ruptured intracranial aneurysms, AVMs, hypertension, intraventricular tumors, bleeding diatheses, cerebral venous thromboses, Moyamoya disease, drug abuse, and infections.² Primary IVH represents only about 10% of all cases of IVH and historically has been associated with poor outcomes. These can be attributed to obstructive hydrocephalus, inflammatory effects of blood products, and direct mass effect of the hematoma.³

Therapies for IVH have evolved over decades. Primary placement of EVDs was attempted but proved to be ineffective due to frequent clotting of catheters. In the 1980s, urokinase was studied in animal models of IVH with good results and was subsequently utilized for the treatment of IVH in some centers.⁴ In the 1990s, this approach shifted toward the study of rt-PA for the treatment of IVH. Recombinant t-PA was thought to enhance normal fibrinolytic process within cerebrospinal fluid pathways and hence was thought to be more physiological.² This hypothesis was studied more systematically in the 2000s in the CLEAR-IVH trial, a phase II trial.¹ Recombinant t-PA was found to produce more effective clot lysis as compared to placebo but carried a nonsignificant increased rate of rebleeding (23% vs 5%). Results from this trial showed an acceptable safety profile for rt-PA and led to the CLEAR-III trial. The

results of the CLEAR-III trial showed that IVT rt-PA administration via surgical catheter did not significantly improve the primary end point of good functional outcome (ie, modified Rankin Scale 0-3).⁵ The study did suggest an overall reduction in mortality by 10% in the intervention arm. Subgroup analysis revealed that in patients with larger volume clots who underwent removal of ≥ 20 mL of blood, there was a significant 10% increase in patients achieving good functional outcome.

Cerebral AVMs are present in about 0.5% of the population and have a 2% annual rupture rate. The rate of rebleeding in the first year is thought to be approximately 6%. The presence of cerebral AVMs was an exclusion criterion in the CLEAR-IVH trial¹ and is thought to be a contraindication to thrombolysis. The prognosis of patients with IVH secondary to AVMs, however, is extremely poor.

Our patient presented with a primary pan-ventricular IVH and had CTA, which did not reveal a vascular malformation. He was treated conservatively with placement of an EVD and was stable for 5 days. Unfortunately, prior to performing DSA, he developed obstructive hydrocephalus associated with a rapid neurological decline in the context of a functional EVD. Without the use of rt-PA, this situation was thought to be potentially fatal. Compassionate use of rt-PA was attempted and led to rapid clearance of the ventricular hematoma with ultimate removal of the EVD. No rebleeding was noted. A small AVM with no clear nidus was found on subsequent DSA.

A good outcome was previously reported by Keefe et al in a case of pan-ventricular IVH secondary to a ruptured AVM with the use of rt-PA.⁶ Other reports of patients with massive IVH secondary to AVMs have shown safety of treatment with rt-PA.^{7,8} It is important to note, however, that there may be significant publication bias, as patients with IVH generally have poor prognosis, and rescue therapies may be unsuccessful but not reported. The aforementioned reports, in addition to the safe and effective use of rt-PA in our patient, lend

support to the idea that the use of IVT rt-PA following an IVH caused by an underlying AVM could be further explored in carefully designed clinical trials

Authors' Note

The research submitted in the following manuscript has been unfunded and has been approved by the institutional review board. S.D. and A.M.M. contributed to design or conceptualization of the study. S.D., A.T., A.M., D.Y., and A.M.M. contributed to analysis or interpretation of the data. S.D., A.M., and A.M.M. drafted or revised the manuscript for intellectual content.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dileep Yavagal is a consultant for Aldegan/CytomedixInc, EV3 Neurovascular/Covidien, and Stryker Neurovascular.

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Informed Consent

The patient's family provided consent for publication of this case report.

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