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### Title Page

### Title

Alteplase for acute ischemic stroke after heparin reversal with protamine - a case report and review

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### **Shortened Title**

alteplase for AIS after heparin reversal with protamine

## Key Words

stroke; alteplase; unfractionated heparin; heparin; reversal; thrombolytics; protamine

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#### Abstract

#### Background

Few patients presenting with acute ischemic stroke (AIS) are eligible for alteplase, especially those receiving ongoing anticoagulation. We describe the first reported case of a patient receiving full-dose intravenous (IV) alteplase for AIS after heparin reversal with protamine.

#### Case

A 73-year-old male presented with AIS. He was treated with IV heparin, tirofiban, loading-dose prasugrel, and aspirin prior to percutaneous coronary intervention (PCI) for placement of a right coronary artery stent. One hour following PCI, he abruptly developed left hemiparesis and dysphagia. The National Institutes of Health Stroke Scale was 12 and aPTT was >150 seconds. Head computed tomography (CT) scan showed no acute pathology, and CT angiogram showed no large vessel occlusion amenable to mechanical thrombectomy. Repeat aPTT, obtained 45 minutes later, was 110 seconds, at which time protamine 40 mg IV was administered. At 144 minutes from last known well time, full-dose IV alteplase (0.9 mg/kg) was administered. Follow-up head imaging at 25 hours showed right pontine and cerebellar AIS with no evidence of hemorrhage. The patient was discharged to inpatient rehabilitation 2 days later. Modified Rankin Scale at 3 months was 3, improved from 5 at discharge.

#### Conclusions

Given the lack of adverse events associated with IV alteplase in our patient, we advocate cautious evaluation for potential reversal of acutely administered anticoagulation to facilitate alteplase administration in severely disabled patients who are not eligible for mechanical intervention, and who would have been excluded from definitive AIS treatment.

# Manuscript

## Background

Acute ischemic strokes (AIS) occur in approximately 795,000 people annually in the United States, and are the leading cause of long-term disability.<sup>1</sup> In AIS patients appropriate for alteplase, increased utilization and earlier administration improve the rate of good functional outcomes.<sup>2</sup> However, given the myriad reasons for exclusion or delay in presentation only 3.4-5.2% of AIS patients receive alteplase.<sup>3</sup> Even in alteplase-eligible patients presenting within 2 hours of symptom onset, 26% do not receive IV alteplase.<sup>4</sup> Therapeutic anticoagulation is a relative contraindication for intravenous (IV) alteplase in patients presenting with AIS.<sup>5,6</sup> Systemic thrombolysis is not recommended when the activated partial thromboplastin time (aPTT) is >40 seconds in the setting of unfractionated heparin (UFH).<sup>5</sup> Reversing an elevated aPTT from heparin with protamine cannot be recommended, given the paucity of controlled trial data supporting this strategy.<sup>5</sup> It seems reasonable, however, to consider such a strategy when no other definitive AIS interventions can be pursued in markedly disabled persons, especially considering the already low percentage of AIS patients receiving alteplase and the associated improvement in functional outcomes.<sup>2,3</sup> We report here the first case, to our knowledge, of a patient receiving guideline-recommended, full-dose IV alteplase for AIS after heparin reversal with protamine.

#### Case Report

We present the case of a 73-year-old male, admitted with non-ST-elevation myocardial infarction (NSTEMI), who received post-procedural protamine for the reversal of heparin to facilitate IV alteplase for AIS. The patient presented to the emergency department (ED) with acutely worsening substernal chest pain that followed 2 days of progressive angina. Past medical history included coronary artery disease (CAD) with four previous coronary stents, ischemic cardiomyopathy, hypertension, hypercholesterolemia, type 2 diabetes mellitus, gastroesophageal reflux, and lower back pain. Home

medications were aspirin, isosorbide dinitrate, losartan, metoprolol succinate, insulin glargine, and pantoprazole. Drug allergies were clopidogrel (rash), HMG-CoA reductase inhibitors (muscle tightness), ezetimibe (muscle tightness), and glyburide (angioedema). Family history was significant for six firstdegree relatives with CAD. The patient denied any tobacco, alcohol, or illicit drug use. The presenting modified Rankin Scale (mRS) score was 1.

In the ED, the patient reported 9/10 substernal chest pain. Initial troponin I was 0.85 ng/mL. Electrocardiograph showed new inverted T waves in leads III and aVF. The patient proceeded to semiemergent cardiac catheterization. Aspirin 81 mg was administered at 0900. Tirofiban was initiated periprocedurally with a loading dose of 25 mcg/kg, followed by 0.15 mcg/kg/minute. He also received a 7000-unit IV heparin bolus at 1014 and prasugrel 60 mg following drug-eluding stent deployment to the proximal right coronary artery (RCA) at 1207. He returned from the procedure at 1215. He was speaking with staff and began eating lunch shortly thereafter. At 1250 he began choking on his food, had slurred speech, and could not move his left side. An Acute Stroke Emergency Response Team (ASERT) call was paged, and the patient was assessed by a neurologist at 1305. Initial National Institutes of Health Stroke Scale (NIHSS) was 12 due primarily to left hemiplegia and dysarthria. Tirofiban was immediately discontinued, pending computed tomography (CT) brain imaging, given the possibility of intraparenchymal hemorrhage; aPTT was >150 seconds at that time due to the heparin bolus he had eceived prior.

Non-contrast head CT showed no intracranial hemorrhage. CT angiography (CTA) of the brain and neck showed no arterial occlusion or stenosis. Brain CT perfusion (CTP) was normal. Given an elevated aPTT (>150 seconds) and recent myocardial infarction, the patient met two relative exclusion criteria for the receipt of alteplase. The risks and benefits of alteplase for AIS, specifically highlighting that the patient was outside the standard of care for IV alteplase administration and therefore potentially at a higher risk of life-threatening hemorrhage, were discussed with the patient and his son.

The shared decision was made to proceed with alteplase after reversing heparin with protamine, and verbal consent was obtained and documented. Protamine 40 mg IV was administered at 1411 for aPTT of 110 seconds. Repeat aPTT at 1439 was 26 seconds. Alteplase 6.5 mg bolus (0.09 mg/kg), followed by 58.5 mg (0.81 mg/kg) IV infusion over 60 minutes was administered at 1512, 2 hours 32 minutes after last known well time. The patient was transferred to the Neuroscience Critical Care Unit and monitored per the acute stroke monitoring protocol for 24 hours.

Magnetic resonance imaging (MRI) without contrast obtained approximately 24 hours after alteplase administration showed a 1 cm by 2.1 cm acute right pontine infarction and punctate areas of acute infarction along the cortical surface of the right cerebellar hemisphere. There was no acute supratentorial brain infarction and no intracranial hemorrhage. Aspirin 81 mg daily was initiated that afternoon, along with ticagrelor 90 mg twice daily, given stent placement. Heparin 5000 units subcutaneously every 8 hours was started for venous thromboembolism prophylaxis. Troponin I levels peaked at 81.76 ng/mL at 1300 the day of his stroke and down-trended consistently over the next 48 hours. He was discharged to an acute inpatient rehabilitation unit 3 days after AIS treatment. Given the myriad comorbidities contributing to his diminished functional status, including NSTEMI, ischemic cardiomyopathy, diabetic neuropathy, chronic lumbar back pain, and AIS, the patient had an mRS score of 5 at discharge. At 3 months post discharge his mRS had improved to 3.

#### Discussion

To our knowledge, this is the first report describing a patient receiving full-dose IV alteplase (0.9 mg/kg) for AIS after heparin reversal with protamine. The patient had no associated complications, including ICH, suggesting that it is possible to safely administer alteplase to carefully selected patients following acutely administered anticoagulation reversal. He also had functional improvement over the 3 months following discharge, though alteplase cannot be confirmed as a contributor to this. In our case,

therapeutic heparin was used peri-PCI to facilitate coronary artery stent placement in the setting of NSTEMI. Similar results, showing safety with alteplase and potential functional improvements have been reported in patients with acute coronary syndromes receiving peri-procedural heparin<sup>7</sup> or low-molecular weight heparin reversed with protamine.<sup>8</sup> The former, however, used low-dose alteplase (0.6 mg/kg).<sup>7</sup>

It is notable that on initial neuroimaging our patient had no evidence of large vessel occlusion by head and neck CTA and no perfusion abnormalities by brain CTP, suggesting small vessel stroke, which was later confirmed by brain MRI. The absence of an identified arterial occlusion by CTA before treatment suggests lower risk of ICH after IV alteplase relative to a scenario of arterial occlusion identified by CTA before treatment.<sup>9</sup> Our patient also had an initial NIHSS of 12, which is associated with lower risk of ICH after treatment with IV alteplase than in patients with NIHSS >20.<sup>10</sup> We likely would have pursued mechanical intervention, rather than reversal of acutely administered anticoagulation followed by full-dose IV alteplase, if our patient had evidence of acute arterial occlusion by head or neck CTA or if his initial NIHSS was >20. Treatment with IV alteplase was initiated 2.5 hours after last known well time in our patient. Alteplase may be administered up to 4.5 hours after last known well time in patients not meeting exclusion criteria. However, it is paramount to administer alteplase as quickly as possible given that with further delays in alteplase administration the odds of a favorable 3-month outcome decrease and the risk of intracranial hemorrhage may increase.<sup>11-15</sup>

Our patient did not require ongoing therapeutic anticoagulation for stroke prevention in atrial fibrillation or for venous thromboembolism treatment. These situations introduce an additional layer of complexity given the underlying thrombotic disease states present, which was not necessarily the case with our patient. Cases where ongoing therapeutic anticoagulation with dabigatran was reversed with idarucizumab to facilitate alteplase administration have been reported.<sup>16-19</sup> In each of these cases the patients were receiving therapeutic anticoagulation for stroke prevention in atrial fibrillation.<sup>16-19</sup> In all

four cases, feasibility of alteplase administration was established with the potential for clinical improvement and without evidence of ICH.

Current guidelines recommend excluding patients from receiving alteplase if heparin is received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal.<sup>6</sup> Indeed, there are only 164 reported cases of patients receiving alteplase for AIS with elevated aPTT.<sup>5</sup> Six of the 164 patients, from all included studies, suffered symptomatic ICH, though all were from the same VISTA registry (6 of 139 patients; OR 1.57, for alteplase vs no alteplase; 95% CI 1.02-2.41; *P*<0.001).<sup>20</sup> Notably, none of these patients received protamine for reversal of heparin prior to alteplase. Given the lack of data, the Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke recommendations are to exclude patients from receiving alteplase with aPTT >40 seconds.<sup>5</sup> Additionally, no firm conclusions can be made regarding the safety or efficacy of IV alteplase after correcting coagulopathies such as elevated aPTT.<sup>5</sup>

Our case highlights the potential safety of alteplase for AIS after heparin reversal with protamine. Unfortunately, biases such as positive outcome selection and positive outcome publication may play a role in which cases are submitted and ultimately published, thus skewing collective results of case reports in favor of a particular intervention.<sup>21</sup> Positive outcome publication bias has not necessarily impacted studies with higher methodological quality such as prospective cohort studies or randomized controlled trials.<sup>22,23</sup> Given the potential for bias with case reports and case series, however, extreme caution is warranted in evaluating patient-specific, theorized risk-benefit analyses for the reversal of ongoing anticoagulation to facilitate alteplase in AIS. There are several viable alternatives to the strategy we describe in our case report. The first is simply withholding alteplase given the relative exclusion criteria of ongoing heparin anticoagulation and recent NSTEMI. This option would be consistent with current guideline recommendations. A second approach may be administering alteplase without reversing heparin with protamine. Lastly, one could wait for the aPTT to decrease to within normal

range then administering alteplase, such as was done in a recently published case report in a patient similar to our own, post-cardiac catheterization.<sup>24</sup> The team decided to recheck the aPTT after one hour because the patient was still within the treatment window (3 vs. 4.5 hour time window not specified). Repeat aPTT was in normal range and thus alteplase was administered. Because delays in alteplase for AIS decrease the possibility of good functional outcome and increase the risk of hemorrhage, <sup>11-15</sup> we decided not to delay alteplase by waiting for the aPTT to fall within normal range, despite the relatively short half-life. The possibility exists that given the many patient-specific factors associated with heparin elimination that our patient's aPTT would not have decreased to within normal limits within the treatment window. None of the above approaches, however, are supported by adequate clinical trial data to guide a thorough risk-benefit analysis. Future large, multi-center registry studies are needed to better understand the relative risk-benefit of administering alteplase for AIS in similar situations.

## Conclusion

Alteplase was safely administered for the treatment of AIS after heparin reversal with protamine in our patient with small vessel AIS. We advocate cautious evaluation for potential reversal of ongoing anticoagulation to facilitate IV alteplase administration in severely disabled patients who are not eligible for mechanical intervention and who otherwise would have been excluded from definitive AIS treatment.

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# Figure 1. Food and Drug Administration 'sedative' approval time line for selected agents

**Figure 1.** From 1970 to 2000, the Food and Drug Administration approved 4-5 agents per decade that have been used for comfort in adult ICU patients. Most of these agents are used off label, except for midazolam, propofol, and dexmedetomidine. Year of injectable formulation approval was used except for clonidine, valproic acid, and second generation antipsychotics.

## Figure 2. Clinical scenarios where valproate, clonidine, and phenobarbital may be administered

**Figure 2.** Valproate, enteral clonidine, and phenobarbital can be used in various clinical scenarios. Some of these scenarios are in common to one another (e.g., facilitate transition to a non-ICU setting), but others are unique to each agent (e.g., clonidine for multimodal pain relief).

## Figure 3. Relationship between clonidine serum concentration and blood pressure response

**Figure 3.** Blood pressure response following clonidine administration may be dependent on serum concentration. Maximal reductions in blood pressure in 6 subjects with essential hypertension were seen with a steady state serum concentration of approximately 1 ng/mL. When steady state serum concentrations exceeded 2 ng/mL there was a net neutral effect on blood pressure. These findings have not been confirmed in ICU patients.

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