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Acute Treatment of Thrombolysis-Associated Symptomatic Intracranial Hemorrhage: A Case Report

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Introduction

Alteplase (recombinant tissue plasminogen activator or rt-PA) remains the only approved treatment (and the quickest way to achieve thrombolyis) for acute ischemic stroke. Even if the most devastating complication of this therapy is symptomatic intracerebral hemorrhage (sICH) in up to 7% of patients, the overall benefits of rt-PA for stroke appear to outweigh the risks.

However, as the development of sICH is associated with a worse outcome, clinicians caring for these patients are faced with the difficult decision what kind of treatment is best for them. Moreover, to date, there are no evidence-based guidelines as to the management of thrombolysis-associated sICH, most probably due to the fact that there is little original research on the question.

Although the American Heart Association suggests empirical therapies to replace clotting factors and platelets, it also acknowledges the fact that there is a lack of evidence to support any specific therapy. Despite the lack of supporting evidence and the fact that some institutions and/or international organizations have developed care pathways for thrombolysis-associated sICH for current use, the most appropriate management of this complication is not yet clear.

Herein we present a case of a male patient with thrombolysis-associated sICH successfully treated by high doses of cryoprecipitate and platelets. The role of replacing clotting factors and platelets in treatment of thrombolysis-associated sICH is also discussed.

Case Report

A 62-year old man, with a history of hypertension and no other vascular risk factor, was admitted to our Emergency Department for sudden aphasia and right hemiparesis (National Institute of Health Stroke Scale, NIHSS 8) which had appeared 90 minutes before. Brain computed tomography (CT) was normal; his blood pressure (BP) was 130/70 mmHg, chest X-ray, EKG and cardiac evaluation were unremarkable, as were blood and urine examinations, including the coagulation parameters: fibrinogen 527 mg/dL (n.v. 150-400 mg/dL), prothrombin time 12 sec (INR 1.12), activated partial prothrombin time 27 sec, D-dimer 112 ng/mL (n.v. 0-243 ng/mL), platelet count $196x10^3/\mu L$.

Therefore, the patient was considered eligible for intravenous rt-PA (0.9 mg/Kg – 10% was administered as a bolus over 1-2 minutes and the remaining 90% as a 1-hour infusion), which was started 125 min after the onset of the neurological deficit.

Thirty minutes after starting the rt-PA infusion, there was a considerable worsening of the neurological status (NIHSS 18). The rt-PA infusion was stopped and an urgent CT scan of the brain evidenced a left fronto-temporal hemorrhagic lesion with remarkable space occupying effect (parenchymal haematoma type 2 in the ECASS classification). Ten units of cryoprecipitate and 8 units of platelets and an intravenous bolus of 10 mg phytomenadion (vitamin K_1) were administered.
One hour later, a control brain CT scan showed expansion of the hemorrhagic lesion with mild midline shift and prepontine cistern obliteration; the fourth ventricle was not detectable.

The situation was critical as there was no Neurosurgery Unit close by. Therefore, in an attempt to limit the bleeding and bridge the surgical time lapse, we decided to administer a further dose of cryoprecipitate (10 units). The patient arrived at the Neurosurgery Unit with the same NIHSS score and a further brain CT scan showed no increase in the size of the hemorrhage.

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No vascular malformation was documented on cerebral angiography and the patient remained stable. Ten days later the patient was discharged from the Neurosurgery Unit and began rehabilitative treatment in Hospital. Serial CT scan documented the regular evolution of the lesion with progressive resorption of the hemorrhage. The patient had an m-Rankin scale of 2 at the three month follow-up.

Discussion

Post-stroke thrombolysis ICH is a complex and heterogeneous phenomenon, involving numerous factors with poorly known etiology.

The choice of haemostatic therapy remains a controversial issue in thrombolysis-associated SICH and the most appropriate management of this complication is currently unclear. Even if some institutions or international organizations have developed care pathways for thrombolysis-associated sICH for current use, there is a lack of evidence-based medicine. Indeed, SICH following thrombolytic therapy for acute ischemic stroke is associated with a high rate of morbidity and mortality.

In the presence of only clinical signs, the thrombolytic infusion should be stopped and the thawing of cryoprecipitate or fresh-frozen plasma and platelets started, even before an immediate CT scan is done. Indeed, time is a crucial factor when beginning thrombolysis and the same urgency is dictated by the necessity to limit damage in the presence of hemorrhage.

The CT scan evidence that most ICH are expanding and bleeding is ongoing suggests a potential window of opportunity for therapy. Reducing early hematoma expansion after sICH might improve clinical outcome, but it remains to be determined whether any current treatment can meet this requirement.

All currently available thrombolytic agents act by converting the inactive proenzyme, plasminogen, into the active enzyme, plasmin. Plasmin digests fibrinogen, fibrin monomers, and cross-linked fibrin (as found in a thrombus) into fibrin-degradation products. The plasminogen activators vary in stability, half-life and fibrin selectivity. The thrombolytic agents that have been reported for use in IV or IA thrombolysis for stroke include urokinase (UK), alteplase, reteplase, tenectaplase, pro-urokinase, and streptokinase (SK). In general, the nonfibrin-selective drugs (e.g., UK and SK) can result in systemic hypofibrinogenemia, whereas the fibrin-selective agents (e.g., rt-PA and r-pro-UK) are mostly active at the site of thrombosis.

Antifibrinolytics, such as aminocaproic acid seem to be a logical antidote to fibrinolytic therapy and have been proposed as an aggressive measure for limiting intracranial bleeding; however the current guidelines do not recommended its use due to the risk of inadvertent prothrombotic activity. If rt-PA may induce systemic fibrinogenolysis, fibrinogen replacement in the form of fresh-frozen plasma or cryoprecipitate would then be a logical choice for patients with low fibrinogen levels.

However, in our experience, very few patients develop fibrinogen levels below 100 mg/dL, suggesting that currently used rt-PA dosing regimens are not likely to induce hypofibrinogenemia and any benefit of such therapy may be limited. On the other hand, the degree of fibrin specificity of rt-PA is limited because there are rt-PA-specific binding sites on platelet membranes and fibrin/fibrinogen degradation products can also activate plasminogen, indicating that fibrinogen replacement (cryoprecipitate or fresh-frozen plasma) may be indicated.

The theoretical basis for the infusion of platelets as a rescue therapy lies in the fact that the clot lysis releases D-dimers which may exert an antiplatelet effect by binding to the platelet fibrinogen receptor. However, intracerebral hemorrhage is a complex and heterogeneous phenomenon which provides, among other pathophysiological mechanisms, the activation of metalloproteinases (by rt-PA), which may lead to increased blood–brain barrier permeability and, consequently, to a worsening of cerebral hemorrhage and edema. Moreover, other factors, such as ischemic injury and oxidative stress, leukocyte infiltration, vascular activation, have been hypothesized to be potential triggers of hemorrhagic transformation of ischemic lesions, both spontaneous or secondary to thrombolytic therapy. This is a multifactorial process that cannot be blocked by replacing clotting factors or platelets.

CT angiography (CTA) can be used to predict hematoma expansion, as many patients with primary ICH show some degree of contrast enhancement within the hematoma itself, suggesting contrast extravasation from an injured blood vessel. It has been shown that this neuroradiological finding, which has been termed the “spot sign,” is an independent predictor of which patients will develop hematoma expansion.

rFVIIa is an approved treatment to stop bleeding in hemophilic patients with antibodies to factor VIII or IX and has also been reported to reduce bleeding in patients without coagulopathy. The interaction of rFVIIa and tissue factor stimulates thrombin generation. rFVIIa also activates factor X on the surface of activated platelets, which leads to an

enhanced thrombin burst at the inury site. Thrombin converts fibrinogen into fibrin, which produces a stable clot.
Although the administration of rFVIIa led to a successful reduction in the risk of hematoma expansion in patients with primary ICH in two randomized clinical trials, it did not change clinical outcome. This could be attributed to an increased rate of thromboembolic events in the treatment arm. Therefore, the AHA guidelines do not recommend the use of rFVIIa in unselected ICH patients. An updated Cochrane review of hemostatic drug therapies for acute spontaneous ICH concluded that not only did rFVIIa not reduce the death rate, or improve functional status, but that it was also associated to a higher risk of serious thromboembolic adverse events.

Two randomized placebo-controlled clinical trials, The Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT) and Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT) are currently using the CTA "spot sign" to guide treatment with rFVIIa by the selection of those patients at higher risk of hematoma expansion.

In clinical practice, if replacement therapy (cryoprecipitate or fresh-frozen plasma and platelets) is not efficacious and the patient's clinical conditions worsen, in the presence of a CTA "spot sign", then, in our opinion, the administration of rVIIa may be a reasonable choice, despite the potential risk of adverse thromboembolic events.

Conclusion

Many of the therapies used in practice, or recommended by guidelines, are not clearly specific for the reversal of fibrinolytic activity. Given the short half-life of thrombolytic agents, the biological effect of the drug may have abated by the time the diagnosis is made. Nevertheless, ICH is a multifactorial phenomenon and the reported common ongoing bleeding suggests that there is a therapeutic opportunity.

Due to the low frequency of sICH after thrombolysis, large multicenter prospective trials will be required to determine which therapy can best arrest and/or prevent ongoing bleeding.

The finding that continued bleeding occurs after diagnosis suggests an opportunity for intervention; it remains to be determined whether any currently available therapy can meet this requirement, or whether novel treatments should be investigated and developed, based on a better knowledge of the pathophysiological mechanisms of ICH.