RESEARCH ARTICLE

The Use of tPA Alone for Fibrinolysis is based on a Misunderstanding that has Cost Many Lives

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Summary

Fibrinolysis has used tissue plasminogen activator (tPA) alone since 1987 when tPA was approved for the treatment of acute myocardial infarction (AMI). However, fibrinolysis involves both tPA, which initiates fibrinolysis, and urokinase plasminogen activator (uPA), which continues and completes it. tPA has only one fibrin binding site where a small tPA bolus is sufficient to activate the first fibrin-bound plasminogen. The other two are activated by uPA, first zymogenic prouPA and then enzymatic two-chain uPA (tcuPA). tPA and prouPA have complementary mechanisms of action, which gives their combination a potent synergistic effect. When 100 mg of tPA are used, tPA becomes a non-specific, activator which is neither effective nor safe resulting in causing fibrinolysis to lose credibility.

The Current State of the Art

The onset of both AMI and ischemic stroke is triggered by an obstructive blood clot or thrombus. Treatment requires restoring blood flow, especially to the microcirculation, as rapidly as possible. If it is achieved within 1-2 hours of symptom onset, AMI mortality can be reduced to 1%.[1]

Fibrinolysis is the fastest method to reperfuse a thrombus-blocked artery. Since 1987 fibrinolytic therapy has consisted of the administration of tPA alone at high iv doses. The results of this treatment, however, were disappointing from the outset[2] as result, over the last decade tPA was replaced by percutaneous coronary intervention (PCI) whenever possible. Although PCI was only more effective than tPA, also was inherently limited by two problems. It is a hospital procedure that is inevitably time-consuming, and secondly it can only open the epicardial vessels which fails to reperfuse the microcirculation of the myocardium more than half the time.[3]

Although PCI was only slightly more effective than tPA IT was also inherently limited by two problems. And yet, its choice for fibrinolysis over the past 33 years has rarely, if ever, been questioned.

The idea that tPA's inefficacy is due to a limitation of fibrinolysis in general is belied by the efficacy of endogenous fibrinolysis. The endogenous concentration of tPA in normal blood plasma is only 5 ng/ml, and most of this is in an inactive complex with a tPA inhibitor. And yet, a TIMI-3 patency was found at the time of the initial catheterization in 15% of untreated STEMI patients.[4] By comparison, with tPA treated patients, a TIMI-3 patency of the infarct artery at 24 hours was found in 45%.[5] Although in the treated patients the tPA blood concentration was almost 1,000-fold higher, only a three-fold difference in patency was seen. This discrepancy can only mean that endogenous tPA could not alone have been responsible for endogenous fibrinolysis. This finding implicates the other plasminogen activator in blood.

Urokinase plasminogen activator (uPA)

The other biological activator is uPA, the native form of which is a proenzyme, prouPA[6], which is stable in plasma in contrast to tPA, an enzyme against which there is a potent inhibitor in plasma, plasminogen activator inhibitor-1 (PAI-1). Therefore, tPA is stored in the vessel wall from where it is released in the presence of a clot.

Despite its plasma stability, prouPA has a short half-life of about 7 minutes. Since about an estimated one third of the prouPA in blood is bound to the outer platelet membrane [7,8] this prouPA portion has a half-life of about 2.5 days (the half-life of platelets). The binding of prouPA to platelets is not via the uPA receptor, common to many other cells, but rather is related to a novel binding protein[9], and this platelet-bound prouPA is active in fibrinolysis.[10]

The fibrinolytic mechanisms of action of tPA and prouPA are complementary, so that in combination their fibrinolytic effect is synergistic[11], which helps explain the efficacy of endogenous fibrinolysis which functions well at such low concentrations.

The enzyme tPA has an exceptionally high binding affinity for fibrin[12], which helps it bind to the clot before it is inhibited. After its release from the vessel wall, tPAt binds to a specific site on the D-domain of fibrin, which promotes its plasminogen-activating activity against this plasminogen one thousand-fold[13], but this promotion is limited to this one site and plasminogen. This initiates fibrinolysis and completes tPA's role in fibrinolysis, its function being quite analogous that of the starter in a car.

Fibrinolysis creates two additional plasminogen binding sites and their respective plasminogens are activated by uPA. The first plasminogen is activated by prouPA[14], and the second by its enzymatic form, two-chain-uPA (urokinase).[15] Therefore, fibrinolysis involves the sequential activation of three fibrin-bound plasminogens, the first is activated by tPA, and the other two by uPA.

As a consequence, tPA the less dominant of the two activators that was chosen for fibrinolysis 33 years ago and tPA's fibrinolytic effects have defined fibrinolysis ever since. The finding that uPA is responsible for about 66% of fibrinolysis was confirmed by gene deletion studies. These showed that deleting the tPA gene in animals had relatively little effect on the efficacy of fibrinolysis, whereas a uPA gene deletion caused significant inhibition of fibrinolysis as well as some fibrin deposition. Deleting both tPA and uPA genes arrested fibrinolysis completely and caused extensive fibrin deposition.[16] Therefore, both activators are needed for full activity, but uPA is the dominant of the two activators. These findings were further confirmed by a second study gene deletion study.

A clinical test of the dual activator fibrinolytic paradigm

In order to determine if a sequential activator combination was more effective in the clinic, a multicenter study in 101 patients with AMI was once completed. Patients were treated with a mini bolus of tPA (5 mg in 91 patients, 10 mg in 10 patients) followed by a 90-minute infusion of prouPA (40 mg/h), in accordance with the natural paradigm. This treatment resulted in a TIMI-3 patency of the infarct artery in 82% of the patients at 24 hours and a mortality of 1%.[17] This was a substantial improvement over the best of the tPA AMI trials, where the 30-day mortality was 6% and the infarct artery 24 h patency was 45%.[18]

A second clinical trial with this fibrinolytic regimen was never done since the development of prouPA was abandoned not long after the PATENT trial. However now, some twenty-five years later, a second trial with this regimen is underway in ischemic stroke in the Netherlands, and a trial in AMI with this regimen is pending in Ukraine.

The cost in lives

Had the PATENT trial regimen been adopted for fibrinolysis in 1995, when it was published, almost one million AMI deaths in the US alone might have been averted, based on this 1% vs 6% mortality difference. Since prolonged tPA infusions, with their associated bleeding risk, are avoided by this regimen, a safer more effective regimen should also be a boon for the treatment of ischemic stroke.

Whatever the actual number of lives that could be saved may be, it is evident that high-dose tPA alone was an unfortunate choice for fibrinolysis. For example, in PATENT a 5 mg bolus of tPA was sufficient (10 mg was too much). And yet, when tPA is used alone, 100 mg is required, illustrating what a weak activator it is in the absence of fibrin-promotion, which is limited to the first fibrin-bound plasminogen.

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