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Mini Review



# Thrombolysis with Tissue Plasminogen Activator (Tpa) Alone has been A Longstanding Mistake

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## Mini Review

Current thrombolytic therapy consists of high dose tPA administered iv for 60-90 minutes. This treatment has had only limited success in acute myocardial infarction (AMI) [1-3], and consequently has more recently been replaced by percutaneous coronary intervention (PCI) as the treatment of choice in AMI [4]. Although PCI is time-consuming and delays coronary reperfusion, better clinical outcomes than with tPA were nevertheless obtained [5]. In the treatment of ischemic stroke, a tPA dose reduction was required due to a 20% intracranial hemorrhage (ICH) incidence when the AMI dose was used [6]. Dose reduction diminished the thrombolytic efficacy and resulted in a reperfusion rate of only about 30% [7], and a 7% incidence of symptomatic ICH remained [8]. As in AMI, PCI is now being used increasingly in stroke JTT [9-11]. Historically, the use tPA for thrombolysis was based on the belief that tPA was responsible for intravascular fibrinolysis, whereas the other natural plasminogen activator, urokinase plasminogen activator (uPA), was responsible for extravascular fibrinolysis where its effect is mediated by its uPA receptor, UPAR. Although this belief is rarely questioned, it is belied by a number of findings such as those from gene knockout animal studies. These showed that knocking out the uPA gene, but not the tPA gene, impairs lysis of a venous thrombus. The tPA gene knockout had little effect on thrombus resolution [12]. Similarly, a uPA but not a tPA knockout resulted in spontaneous fibrin formation, and uPA mediated fibrinolysis was not impaired by deletion of the UPAR gene [13], contrary to what had been believed.

The tPA dominance concept was implicitly challenged by these findings and also by the unexpected difficulty that was encountered to show that tPA was a better thrombolytic than streptokinase (SK), a non-specific, indirect, and inherently flawed plasminogen activator. An unprecedented total of 95,740 patients with AMI, in three mega-trials, were required to show a statistically significant difference [1-3]. Bayesian analysis of these findings suggested that "the clinical superiority of tPA over SK remains uncertain" [14]. Although there is little uPA in plasma, which reinforced the idea that it was an extravascular activator, there is a significant reservoir of uPA on the surface of platelets [15, 16] and monocytes [17], and uPA's half-life is 2.5 days rather 7 minutes. It is also noteworthy that fibrinolysis involves the activation of three different fibrin-bound plasminogens [18], and only one of these is activated by tPA at a fibrin-specific doses [19]. The other two are activated by uPA, one by prouPA and the other by tcuPA [20-22]. Only at high non-specific doses can tPA activate these two plasminogens, and without its fibrin promotion, tPA is a poor plasminogen activator.

These findings help explain the disappointing results obtained with tPA monotherapy. In addition, since tPA is an enzyme, it is also ill-suited for administration by infusion, and due to its high fibrin affinity, this is unnecessary for its therapeutic effect. In biological fibrinolysis, tPA is stored in the vessel wall, and in the event of intravascular thrombus formation, it is released at that site, binds to the fibrin clot, and initiates thrombolysis. Lysis creates two new plasminogen binding sites on fibrin [23]. Plasminogen on one of these is activated specifically by prouPA [20, 24] which is itself activated to tcuPA in the process [21], and tcuPA activates the remaining plasminogen [22]. Therefore, the two activators are complementary, with thrombolysis being initiated by tPA

and completed by uPA [25]. Using tPA alone for thrombolysis is somewhat analogous to trying to run a car on the starting motor. The activators are also synergistic [25] and this was once tested in a clinical study of 101 patients with AMI. Patients were given a mini-bolus of tPA (5 mg) followed by an infusion (40 mg/h) of prouPA. A TMI-3 infarct artery patency of 60% was obtained, with no reocclusions or ICH and only a 1% mortality [26], results which compare very favorably with the best of the tPA trials in AMI [3, 27]. Therefore, a small bolus of tPA, 5% of the standard dose, was sufficient in the presence of the other activator for exceptionally effective and safe thrombolysis, as also shown experimentally in vitro (Figure 1).

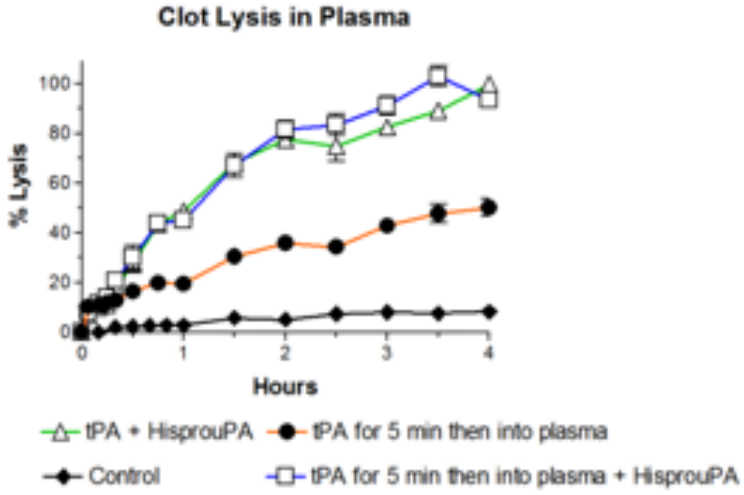


**Figure 1:** 5 minute exposure of clot to tPA (0.2 µg/ml) followed by wash and then clot put into plasma containing HisprouPA (6 µg/ml) (blue) induces same lysis as when tPA is in plasma throughout lysis (green).

Unfortunately, the above clinical study could not be followed up since prouPA commercial development was abandoned not long thereafter. This was because at the therapeutic doses required when used alone, prouPA became unstable in blood and converted to tcuPA, resulting in bleeding complications. To deal with this problem, a more stable, single site (Lys300→His) mutant prouPA was developed which allows the physiological properties of prouPA to be preserved at therapeutic doses [28-38].

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## Conflict of Interest

No conflict of interest.

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