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Opinion Article

More Effective, Safer, and Faster Fibrinolysis

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Opinion

Acute myocardial infarction (AMI) and ischemic stroke are leading causes of death and disability worldwide. Since both the heart and brain's function are dependent on a continuous blood supply, an arterial occlusion can represent a mortal threat to organ function and life itself and reopening the vessel as rapidly as possible is a therapeutic emergency. Therefore, it is surprising that the current treatment of choice for AMI is percutaneous coronary intervention (PCI), and for stroke is thrombectomy when possible. These are technically demanding inpatient procedures that are time-consuming during which salvageable ischemic tissue becomes lost irreversibly to necrosis.

The fastest method by which an occlusive thrombus can be removed, and circulation restored, is fibrinolysis or thrombolysis, which is a natural defense pathway. Unfortunately, this pathway has long been misunderstood and equated with tissue plasminogen activator (tPA) which was believed to be largely responsible for its effect. Therefore, tPA was developed and approved for AMI treatment in 1987. However, when tPA was tested against the previous plasminogen activator, Streptokinase (SK), it performed surprisingly poorly. Comparative trials in a total of 95,740 AMI patients were required in order to reach a significant mortality difference between tPA and SK, and this was seen only in one of four groups in the last of the three trials. A subsequent Bayesian analysis concluded that tPA was not shown to be significantly better than SK [1]. Since SK is a weak plasminogen activator due to its indirect mechanism of action, in which SK first has to form a complex with plasminogen or plasmin and this complex becomes the activator`. Forvthis outcome was especially surprising. hemorrhages than SK in these trials. When tPA was later used in ischemic stroke, 7% incidence symptomatic intracranial hemorrhage complications was found [2]. It was the disappointing efficacy of tPA in AMI that was responsible fo its replacement by percutaneous coronary intervention (PCI), slowing down reperfusion considerably. This enabled PCI to become the treatment of choice after large comparative trials showed it to be more effective than tPA [3]. However, PCI was never compared with any other fibrinolytic. Instead, fibrinolysis was abandoned and replaced by replaced placed by PCI for the treatment of AMI, which eliminated the fastest reperfusion method from further consideration.

This decision was also made before fibrinolysis was understood completely, because therei is a second plasminogen activator involved called urokinase plasminogen activator (uPA). The native form of uPA is a proenzyme (prouPA), which has fibrin-specific properties like tPA, but with a complementary mode of action. As a result, the combination of tPA and prouPA has a synergistic more potent fibrinolytic effect [4]. tPA's function is limited to the initiation of fibrinolysis, analogous to the starter in a car, whereas uPA is responsible for remaining two-thirds of the fibrinolysis. Therefore, the effect of tPA alone, which has been called "fibrinolysis" is not the same and is a lot less potent.

This is because there are three different plasminogens bound to each fibrin monomer that need to be activated to complete fibrinolysis. tPA activates the first one which js close tPA's fibrin binding site. The remaining two plasminogens are activated by uPA, the first by prouPA and the second by its enzymatic form derivative, two-chain uPA (tcuPA). Not surprisingly, fibrinolysis involving all three plasminogens is significantly more effective than tPA alone.

This concept was tested in a clinical study: 101 AMI patients were treated with a small, 5 mg bolus of tPA to initiate fibrinolysis. This was followed by a 90-minute infusion of prouPA (40 mg/h x 90 min) to continue it. This combination was well tolerated and caused few side effects, and the results were consistent with expectations. Compared with the best of the tPA alone studies, this combined regimen almost doubled the infarct artery patency rate and reduced AMI mortality 6-fold [5].

These clinical results are consistent with in vitro findings showing the activators' complementary and synergistic fibrinolytic effects. These findings also show that the effects of tPA alone, which has represented fibrinolysis for 33 years, greatly underestimates the true efficacy of fibrinolysis. Fibrinolysis requires both activators and using only tPA is something altogether different and is only one third as effective.

Therefore, the findings and conclusions coming out of the many comparative studies against fibrinolysis by tPA alone are not valid.

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