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Short Communication

More Effective, Faster, and Safer Fibrinolytic Treatment of Heart Attack and Ischemic Stroke

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Acute myocardial infarction (AMI) and Ischemic stroke are among the commonest cardiovascular pathologies and both of them are usually triggered by an occlusive blood clot or thrombus. Since the brain and heart are highly dependent on an uninterrupted blood perfusion, their functional survival as well as mortality depend on a rapid restoration of the blocked blood supply. Therefore, it is surprising that the current treatment of choice for AMI and ischemic stroke is percutaneous coronary intervention (PCI) or thrombectomy for stroke, when possible. These are technically demanding hospital procedures that is time-consuming, during which salvageable ischemic heart and brain tissue will be irretrievably lost to necrosis.

The simplest and fastest method by which an occlusive thrombus can be removed, and perfusion restored is fibrinolysis, which is a natural defense against thrombosis. Unfortunately, it has been believed that tissue plasminogen activator (tPA) is responsible for fibrinolysis, and therefore tPA was developed and approved for treatment more than thirty years ago. However, when tPA was tested in comparative trials against the older drug, Streptokinase (SK) it proved to be little better than SK as confirmed by a subsequent Bayesian analysis [1]. This unexpected inefficacy of tPA was the first indication that the plasminogen activator itself, whether it be tPA or SK, made little difference to the efficacy of fibrinolysis. Therefore, changing the activator was not going to help improve fibrinolytic therapy. When used for ischemic stroke, tPA was associated with a 7% rate of symptomatic intracranial hemorrhage complications, higher than that of SK [2]. Eventually these results led to the replacement of tPA by PCI for AMI and thrombectomy for stroke when possible. These in-hospital catheterization procedures slowdown reperfusion considerably [3], and has made reperfusion treatment more costly and slower.

The reason that tPA alone for fibrinolysis failed is based on a misunderstanding of this natural system. In blood there are two plasminogen activators, tPA and prouPA and both are required for full and effective fibrinolysis, and the natural system also utilizes both of them in sequence starting with tPA. The other activator, prouPA, which is a proenzyme is stable in blood, in contrast to urokinase which has been known as long as tPA but was not considered an activator because urokinase was rapidly inhibited by a blood inhibitor. ProuPA is the native form and has fibrinolytic properties complementary to tPA as a result of which the combination of tPA and prouPA has a synergistic more potent fibrinolytic effect [4,5]. In the combination, tPA's function is limited to one third of fibrinolysis, whereas uPA is responsible for two-thirds of the fibrinolysis.

The clinical efficacy of this sequential combination of tPA and prouPA was tested in a clinical trial of 101 patients with acute myocardial infarction (AMI). Treatment was initiated by a 5 mg bolus of tPA [5% of the dose needed when tPA is used alone], which was followed by a 90-minute infusion of prouPA (40 mg/h). This regimen almost doubled the infarct artery patency rate of that induced by tPA alone. It also reduced AMI mortality rate from 6% to 1% [6]. These clinical results represent an unambiguous confirmation of the importance of using both activators instead of only tPA as shown in clot lysis studies with tPA and prouPA in vitro.

Unfortunately, Farmitalia, the sponsor of this trial was sold shortly after this trial and despite its unprecedented results, this trial was never repeated to date.

Conclusion

These findings show that the results obtained with "fibrinolysis" by tPA alone over the past 33 years were inadequate because prouPA, the second activator, was missing, and tPA alone is limited to the activation of only one of three fibrin-bound plasminogens involved in fibrinolysis. Using both activators in sequence is not only more effective but is also safer since on 5% of the standard dose of tPA is needed and only 50% of that used in monotherapy with prouPA. As a result there is little risk of bleeding side effects.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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