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Review Article

PCI is Too Slow and Limited to Treat Vascular Emergencies

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Introduction

The current treatment of choice for a vascular-obstructive disorder like AMI or ischemic stroke, is an interventional procedure like percutaneous coronary intervention (PCI). This treatment requires getting the patient to a hospital equipped with an available catheterization laboratory. This is likely to delay reperfusion for at least two hours or more, and any delay in reperfusion is well known to be correlated with an increase in AMI morbidity and mortality. Moreover, PCI is a procedure that is costly, and receives an average reimbursement of as much as $23,700 in the USA. Since AMI and stroke are conditions that are as common in poor as richer countries, the cost of PCI and lack of access in rural areas may put this treatment out of the reach of many populations in need. A critical reexamination of whether an invasive treatment like PCI is the best treatment of choice for AMI and stroke seems warranted. Historically, interventional procedures, like PCI, replaced fibrinolysis or thrombolysis, because both were considered insufficiently effective. However, despite this perceived liability, true endogenous fibrinolysis has a number of advantageous properties. The most important of these is that physiological fibrinolysis is significantly faster, by at least a couple of hours. Secondly, fibrinolysis is not limited to vessels that are larger than the catheter. Third, fibrinolysis is significantly less expensive and requires no additional manpower. Finally, due to the discovery of a high affinity tPA fibrin binding site located next to plasminogen Aa 157 on the fibrin D-domain, only a 5 mg mini dose of tPA is needed to activate this plasminogen and initiate fibrinolysis [1]. At this low tPA dose, there is no risk of non-specific fibrin binding, which can cause bleeding.

tPA was discovered in 1947 and is the only physiological plasminogen activator that binds to fibrin. The physiological fibrin binding site is located adjacent to the plasminogen binding site on the D-domain of fibrin on A site that is responsible for initiating fibrinolysis. Then in 1981, a second endogenous plasminogen activator was isolated from recently voided urine in my lab (Dr. Gurewich). Since for about 75 years, urine was known to contain only urokinase (UK), a two-chain enzyme which was assumed to be a waste product, the finding of a new form of UK, which was a single-chain pro-enzyme, was greeted with skepticism, which delayed its publication for about three years [2]. Even today, whereas tPA is almost a household name, proUK remains relatively unknown. At the same time, gene deletion studies showed that a proUK deletion virtually eliminates the fibrinolytic system, whereas a tPA deletion has almost no effect on fibrinolysis. In addition, proUK has a double lytic effect, that by the intrinsic activity of proUK, and that by UK. By contrast, tPA has only a single activity. However, what is harder to address is that the clinical experience with fibrinolysis

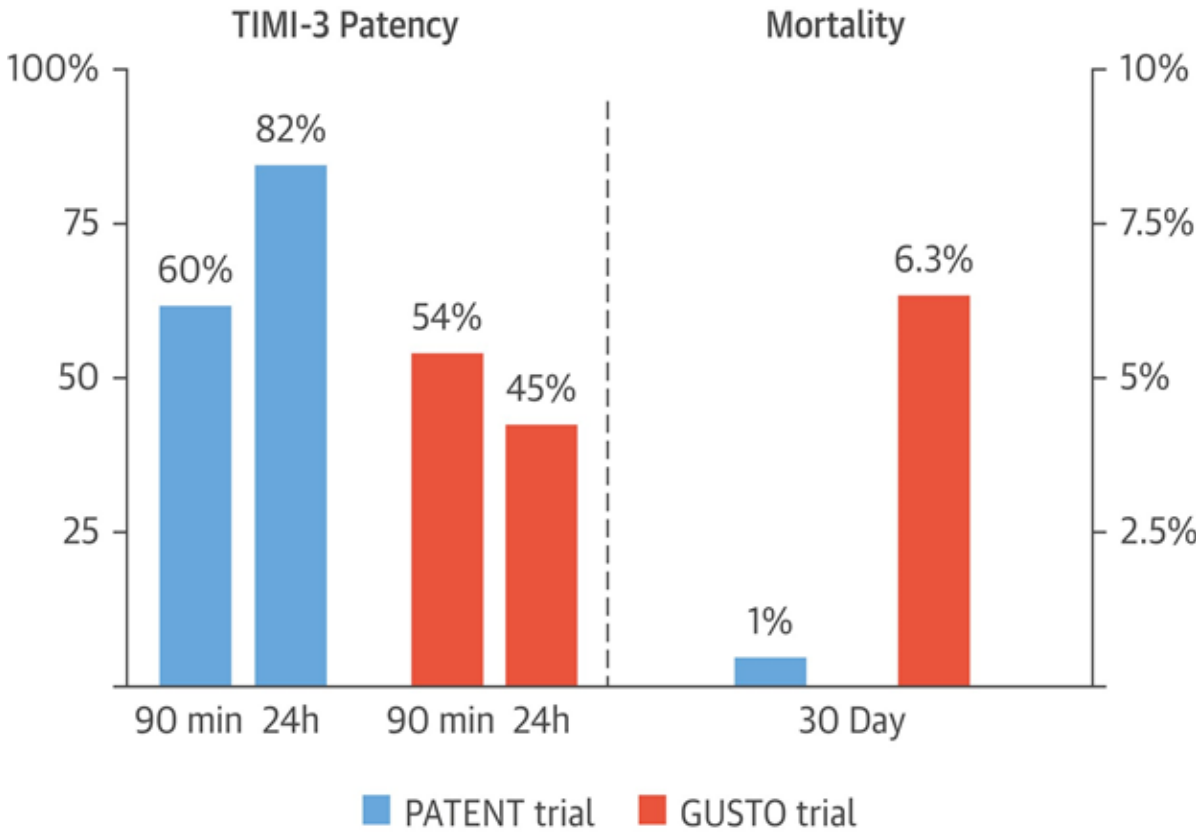

Figure 1: PATENT Trial [3].

seems to have left some anti-fibrinolysis bias. How else to explain the resort to a slow, complicated interventional procedure to treat a condition like AMI where the time to reperfusion is so important? For example, in the forty-thousand patient GUSTO trial,15% of the patients, prior to receiving any treatment, had completely patent infarct arteries, meaning that endogenous lysis had already taken place. This is a testimony to the lytic power of even a nanogram combination of tPA and endogenous proUK. This endogenous biological combination is also a promising model for "new" physiological fibrinolytic therapy. However, there is little evidence to date that this observation, especially the tPA/proUK synergy, has attracted the interest that it should have.

An example of this combination is the PATENT trial (Figure 1) in which 101 AMI patients were treated with a small bolus of tPA followed by a 90 minute infusion of proUK. The results were unprecedented with an 82% complete TIMI-3 patency of the infarct artery and a 1% mortality, compared to 6% when AMI was treated with tPA in the GUSTO trial [3]. Due, at least in part, to the lack of availability of proUK, this successful combination has not been repeated or adopted. Since true, physiological fibrinolysis requires both tPA and proUK and involves the activation of all three fibrin-bound plasminogens, tPA used alone is not full fibrinolysis. To our knowledge, PCI has never been compared with full fibrinolysis of tPA and proUK. This test needs to be done before PCI is assumed to be the standard of care for STEMI patients.

This is particularly important since there is no question that fibrinolysis induces significantly faster and more comprehensive reperfusion throughout the cardiac vasculature than PCI or any other interventional procedure, and all else being equal, earlier reperfusion is significantly more effective.

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