A Novel Role for Tissue-Type Plasminogen Activator: Prevention of Thromboembolic Occlusion

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Activation of plasminogen by agents such as tissue-type plasminogen activator (tPA), yields plasmin, lyses fibrin, and thereby restores flow to blood vessels occluded by thrombi. Because tPA binds to fibrin, as does plasminogen, at low doses, tPA-mediated generation of plasmin is localized, rendering tPA clot selective. This result, plus its short half-life (4.5 minutes), led to the hope that its use would not only enhance coronary and cerebral thrombolysis but also reduce the risk of bleeding, including intracranial hemorrhage. At high conventionally used doses, clot selectivity is incomplete. Perhaps that is why treatment with tPA compared with a non-clot-selective agent, streptokinase, reduced mortality in patients with ST-elevation myocardial infarction but did not diminish the incidence of intracranial hemorrhage.

In this issue of Circulation, Danielyan and colleagues describe a novel use of tPA, prevention rather than treatment of thrombi-occluding vessels resulting from emboli. Linkage of tPA to red blood cells (RBCs) prohibited its penetration into protective established thrombi, facilitated lysis of nascent thrombi induced by embolization of fibrin, and markedly prolonged the half-life of tPA in the circulation. Compared with soluble tPA, RBC-coupled tPA (RBC/tPA) more effectively lysed nascent cerebral thromboemboli and diminished hemorrhagic complications.

Nascent thrombi are lysed with particular efficacy by very low concentrations of tPA probably because cross-linking of fibrin is limited in such thrombi. Consistent with the observations of Danielyan et al, Fox and colleagues found that “subthrombolytic” concentrations of tPA prevented formation of an occlusive thrombi. In the Danielyan study, the prolonged half-life of RBC/tPA enabled lysis of emboli when mice were treated with RBC/tPA as long as 1 hour before injection of fibrin emboli. A 10-fold-lower concentration of tPA compared with soluble tPA restored and maintained blood flow.

Clot lysis is not necessarily enhanced by increasing concentrations of tPA. Depletion of plasminogen by high concentrations of tPA can paradoxically inhibit lysis, a phenomenon referred to as plasminogen steal. Consequently, concentrations of tPA sufficient to deplete plasminogen may actually decrease lysis. Because lower concentrations of tPA can be used when infused as RBC/tPA, lysis of nascent but not established protective thrombi should limit depletion of plasminogen and thereby potentially enhance lysis as observed by Danielyan and colleagues.

Although a prolonged infusion of soluble tPA would be expected to lyse nascent thrombi effectively, such an infusion would be associated with a high risk of bleeding after surgical procedures. Coupling of tPA with RBCs prevents its penetration into hemostatic clots and was not associated with bleeding at the surgical site when injected 10 minutes after tail amputation in mice. This result is consistent with the observed preservation of fibrinogen in blood and is consistent with an absence of plasminemia and a systemic lytic state. The absence of a systemic lytic state combined with the preclusion of penetration of RBC/tPA into hemostatic plugs appears to account for the lack of bleeding seen with RBC/tPA.

Plasmin is not only a pivotal mediator of intracranial hemorrhage, it can also induce neurological damage directly. Plasminemia accentuates cerebral hemorrhage and may degrade vessel wall extracellular matrix and vitiate the integrity of the blood brain barrier independent of induction of hemorrhage. Accordingly, the capacity of RBC/tPA to lyse nascent thromboemboli with low concentrations of tPA and avoidance of plasminemia is likely to be neuroprotective and to limit the risk of hemorrhage.

Perhaps counterintuitively, tPA can activate prothrombin. Thus, use of soluble tPA can generate not only plasmin but also thrombin. Both thrombin and plasmin contribute to neuropathic changes after an ischemic insult. Additional benefits associated with use of the lower concentrations of tPA when coupled with RBCs are likely to contribute to a lower incidence of neurological damage after ischemia.

Properties of RBC/tPA and its potential for prophylactic use in patients at high risk of embolic stroke make the observations by Danielyan and colleagues particularly promising. However, the enthusiasm must be tempered because the studies were done in mice, the report is an initial study in vivo, the cerebral vascular insults were induced with fibrin emboli, and the animals were healthy. As noted by the authors, mouse plasminogen differs from human plasminogen with respect to its susceptibility to activation by tPA. Its relative resistance to activation may have limited induction of a systemic lytic state by RBC/tPA. Subsequent studies in other species and ultimately in patients will be necessary to determine whether concentrations of RBC/tPA that effectively prevent thromboembolic occlusion of vessels are not...
associated with induction of plasminemia and the associated risk of bleeding.

In the Danielyan study, mice treated with RBC/tPA 10 minutes after amputation of the tail did not bleed from the surgical site. This observation suggests that thromboprophylaxis with RBC/tPA may be initiated very early after surgical hemostasis has been achieved and raises the possibility that surgical hemostasis may be achievable even after treatment with RBC/tPA has been implemented. For surgeries in which a minor amount of bleeding would be dangerous, such strategies would be unattractive. However, cardiac surgery is performed safely and generally for patients already being treated with aspirin. Thus, if surgical hemostasis can be achieved in the face of therapeutic concentrations of RBC/tPA, the implications would be substantial. For example, extracorporeal circulation during cardiac surgery is associated with activation of the coagulation cascade and platelets. Treatment with RBC/tPA under the circumstances might reduce the incidence of microembolization and neurological deficits including the cognitive dysfunction that follows cardiac surgery. Percutaneous coronary and cerebral arterial vascular procedures have been associated with distal microembolization. RBC/tPA might diminish the incidence of such sequelae.

Validation of clinical use of RBC/tPA will require either the cross-linking of tPA to autologous RBCs or the use of allogeneic RBCs that are type specific. The logistic demands associated with the use of autologous RBCs favor the use of allogeneic RBCs. The non-RBC components of transfusion products appear to account for the majority of prothrombotic and proinflammatory effects of transfused blood. Accordingly, type-specific allogeneic RBC/tPA should impart only modest additional risk with respect to the RBC component.

In summary, the development of RBC/tPA is promising. Linking tPA with RBCs prolongs the half-life of tPA and confines tPA to the vascular space. These features favor lysis by tPA of nascent but not established hemostatic thrombi. Because the lower concentrations of tPA that can be used do not induce plasminemia nor activate thrombin, the risks of bleeding and neurological injury are reduced. If the initial results in mice reported by Danielyan and colleagues can be reproduced in patients, reduction of thromboembolic complications may indeed be achievable.

Disclosures
None.

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