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The traumatic side of fibrinolysis

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In this issue of Blood, Hijazi et al challenge the view that consumptive coagulopathy that accompanies traumatic brain injury (TBI) results in a sequence of events that lead to intracranial hemorrhage (ICH).1 Why is it that an antifibrinolytic drug that is given to reduce bleeding in severe trauma patients can sometimes cause the very thing it is intending to stop? The paper highlighted in this commentary provides an interesting insight that goes a considerable way toward explaining this paradox and also how the fibrinolytic system can be inadvertently turned on when it should be turned off.

One of the greatest causes of mortality associated with TBI is ICH. Consumptive coagulopathy that accompanies TBI is widely assumed to underlie the sequence of events leading to ICH expansion. Not only do Hijazi et al challenge this view, but they imply that coagulopathy is not a cause of ICH at all but rather occurs as a consequence of the fibrinolytic system being activated within the brain.

To explore the role of the fibrinolytic system in the promotion of ICH following TBI, wild-type (WT) mice and mice deficient in tissue-type plasminogen activator (tPA) or urokinase plasminogen activator (uPA) were subjected to a closed head injury model of TBI, and the degrees of ICH and coagulopathy were evaluated. WT mice had an increase in plasma D-dimer levels and a drop in platelet count within 2 hours, but there was no change in the international normalization ratio (INR),

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indicating normal clotting parameters. Hence, this model of TBI causes only a mild coagulopathy. Nonetheless, the extent of ICH steadily increased over time but did not correlate with D-dimer levels or platelet count. Instead, the extent of ICH correlated with an increase in fibrinolysis, but the interest here is in the detail. Fibrinolytic activity increased in the cerebrospinal fluid but not in the blood of injured mice. However, both tPA^{-/-} and uPA^{-/-} mice developed less ICH after TBI, but only tPA^{-/-} mice became coagulopathic; D-dimer levels and platelet counts were essentially unchanged in uPA^{-/-} mice. Urokinase was therefore causing a pronounced effect on the hemostatic system. To further support the role of the fibrinolytic system in promoting ICH, the authors forced coagulopathy by anticoagulating mice with warfarin. Warfarin increased the INR to a similar extent in WT, tPA^{-/-}, and uPA^{-/-} mice, but only WT mice developed a greater degree of ICH following TBI. The lack of ICH expansion in warfarin-treated tPA^{-/-} or uPA^{-/-} mice strengthens the idea that both uPA and tPA were driving ICH. The capacity of both u-PA and t-PA to promote ICH and the increase in ICH seen in anticoagulated WT mice were inhibited by an inactive t-PA variant (tPA-S481A).

Together, these findings are relevant considering current efforts to attenuate consumptive coagulopathy in severe trauma patients using antifibrinolytic drugs. Most prominent here is the use of the lysine analog tranexamic acid (TXA). The CRASH-2 trial suggested a net benefit of TXA to worsen ICH. Clearly, any new antifibrinolytic approaches aimed at reducing ICH following TBI should be tailored to annul the effects of both tPA and uPA. So, at the end, there is really no paradox. What appears to be happening is actually consistent with what was already known about the differential effects of TXA on ICH in mice.

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