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Hemophilia rarely becomes symptomatic during the neonatal period

Excessive bleeding during delivery and in the neonatal period is a relatively rare event in hemophilia. In a French study of 754 neonates with hemophilia, only 8% showed clinically overt bleeding; the diagnosis was made after the neonatal period in 71.5% of patients (Chambost). Intracranial bleeding is found in only 3.6% (Kulkarni) to 3.9% (Ljung) of neonates with hemophilia. These findings are surprising since delivery causes bleeding in neonates without a disorder of hemostasis. The trauma of delivery should therefore be sufficient to trigger bleeding in severe hemophilia.

The low incidence of bleeding of patients with hemophilia in the neonatal period is probably explained by the peculiarities of the neonatal hemostatic system. Healthy term neonates have low levels of many clotting factors and inhibitors, especially prothrombin complex and contact factors, antithrombin, protein C and S, and tissue factor pathway inhibitor (TFPI). Using the Hemker method, the thrombin potential of healthy neonates is about 40% of that of adults, a value that would render adults prone to excessive bleeding. But healthy neonates have an excellent hemostasis and good wound healing. The discrepancy between clinical and in vitro findings are not completely understood.

We have previously used the Hemker method to show that the efficient hemostasis in neonates was not fully explained by low levels of antithrombin, protein C and protein S when conventional reagents such as thomboplastin were used in activation (Cvirn 2000, 2001, 2002). Recent work from our laboratory showed that when small amounts of tissue factor were used in place of conventional activators, clotting times of neonatal plasma were shorter than those of adult plasma. Thrombin generation and Xa-generation started earlier and reached higher values in neonatal plasma than in adult plasma. This was caused by the combined effects of low antithrombin, TFPI, and protein C/S in neonatal plasma (Cvirn 2003, J Thromb Haemost.1, 263-68). If one assumes that activation by small amounts of tissue factor is more physiological than activation by thromboplastins, our findings help to explain the efficient hemostasis despite low clotting factors in healthy neonates.

In the proposed project we would like to expand our investigations to the plasma of neonates with severe hemophilia A and B. Artificially depleted cord plasma can be substituted for preliminary investigations. As described above, we would like to compare the effects of various inhibitors on the generation of thrombin and factor Xa in the plasma of neonates and adults with hemophilia. Our findings might not only help to explain the observed rare bleeding in neonates with hemophilia, but also help to understand differences in bleeding manifestations potentially caused by different inhibitor levels in later life. The award should cover the costs of a full-time research fellow (PhD or MD) and reagent costs. Facilities at our institution can be used without any overhead.

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