Augmentation of Thrombin Generation in Neonates Undergoing Cardiopulmonary Bypass

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INTRODUCTION

Recombinant activated factor VII (rFVIIa; Novoseven®, Novo Nordisk, Bagsvaerd, Denmark) is increasingly being used off-label for treating refractory bleeding after complex congenital cardiac surgery. However, the therapeutic response to rFVIIa may not be optimal in post-CPB patients who develop multiple coagulation factor deficiencies. However, it is plausible that the replacement of prothrombin and factor (F) X can restore thrombin generation without adding much FVII (1). Three factor-prothrombin complex concentrates (3F-PCCs) that contain prothrombin (FII), FX, FIX and low amounts of FVII are available in the United States. In this investigation, we compared in vitro the efficacies of rFVIIa and 3F-PCC in improving thrombin generation in neonatal plasma after CPB.

METHODS

After approval by the Institutional Review Board, ten neonates were enrolled in this prospective study. Three blood samples were obtained from each neonate: pre-CPB, immediately post-CPB and post-products after the transfusion of a quarter of a unit of apheresis platelets and three units of cryoprecipitate. Lagtimes or the time to initiate thrombin generation and peak thrombin levels were measured in vitro using a calibrated automated thrombin generation assay [Thrombinoscope, Stago, Maastricht, Netherlands (2)]. The pre-CPB sample provided a baseline measurement. The post-products sample was divided into three aliquots: control, control plus a therapeutic concentration of rFVIIa, control plus a therapeutic concentration of 3F-PCC (Profilnine, Grifols Biologicals Inc., Los Angeles, CA).

RESULTS

Lagtimes and peak thrombin levels are shown in Table 1. Lagtime remained prolonged compared to baseline for all subsequent measurements; however, rFVIIa did shorten lagtime from the post-CPB and post-product values. Conversely, the addition of 3F-PCC, but not rFVIIa, resulted in a statistically significantly increase in peak thrombin levels when compared to baseline. The transfusion of platelets and cryoprecipitate, rFVIIa and 3F-PCC all significantly increased peak thrombin levels when compared to post-CPB, with the increase from 3F-PCC being the greatest.

CONCLUSIONS

3F-PCC increased thrombin generation more than rFVIIa. The reduction of the post-products lagtime by 3F-PCC was numerically similar to rFVIIa although it was not statistically significant. We hypothesize that the greater effect of 3F-PCC is a result of its ability to augment levels of prothrombin, FIX and FX. However, the thrombotic risk associated with 3F-PCC is unclear. A greater understanding of the procoagulant effects of 3F-PCC in neonates undergoing cardiac surgery is needed so that a well-designed randomized controlled trial can be performed to evaluate its efficacy.

REFERENCES

1. Blood 2010;116(5):693-701
2. Thromb Haemost 1993;70:671-4

Table 1: Thrombin Generation Measurements

	Lagtime (mins)	Peak Thrombin (nM)
Baseline	2.3 ± 0.6	143.5 ± 80.8
Post-CPB	3.8 ± 1.2*	161.6 ± 71.2
Post-products	3.2 ± 0.3*	191.5 ± 57.2*#
Post-products + rFVIIa	2.9 ± 0.2*+	194 ± 48.9*#
Post-products + 3F-PCC	2.9 ± 0.3*	423.3 ± 38.1*#+

CPB = cardiopulmonary bypass; rFVIIa = recombinant activated factor VII; 3F-PCC = 3 factor-prothrombin complex concentrate

*p < 0.05 versus baseline
#p < 0.05 versus post-CPB
+p < 0.05 versus post-products