short report
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INEFFICACY OF FRESH FROZEN PLASMA IN THE TREATMENT OF L-ASPARAGINASE-INDUCED COAGULATION FACTOR DEFICIENCIES DURING ALL INDUCTION THERAPY

Ulrike Nowak-Göttl, Bertha Rath, Martha Binder, Jörg-Ullrich Hassel, Johannes Wolff, Stefanie Husemann, Jörg Ritter

Center of Pediatric Hematology and Oncology, University Hospital Münster, Germany

ABSTRACT

A prospective longitudinal study was conducted to determine whether single-donor fresh frozen plasma (FFP) substitution was able to influence L-asparaginase-associated hypoproteinemia. Within a 36-month period, 20 of 42 children with ALL received a total of 42 prophylactic FFP doses at a median of 10 (5-20) mL/kg when fibrinogen levels decreased to <60 mg/dL and thrombin time was lengthened. Laboratory monitoring before, during and after FFP substitution showed no short-term improvements and demonstrated only a minimal increase in fibrinogen and α_2-antiplasmin. Plasma levels of antithrombin and plasminogen remained unchanged. Furthermore, administration of FFP had no influence on thrombin generation, the plasmin/α_2-antiplasmin complex or enhanced D-dimer formation.

Key words: fresh frozen plasma, fibrinogen, antithrombin, thrombin generation, D-dimer formation

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Combination chemotherapy in childhood acute lymphoblastic leukemia (ALL) using prednisone, vincristine, daunorubicin and asparaginase (ASP) has dramatically increased the cure rate.[1] Among the treatment-related side effects hemostatic toxicity is of major concern. In particular, the concentrations of several coagulation proteins such as fibrinogen, plasminogen, antithrombin, and protein C are greatly diminished by treatment with L-asparaginase.[2,3] Furthermore, the incidence of hemostatic alterations in patients with ALL appears to depend on the treatment schedule and the ASP preparation used.[4,5]

Besides thrombotic events, hemorrhages and acquired L-asparaginase-induced hypofibrinogenemia and evidence of DIC have also been reported in children with ALL.[6-8] In order to evaluate the possible effect of fresh frozen plasma (FFP) on coagulation and fibrinolytic proteins associated with bleeding tendencies, a prospective longitudinal study was conducted.

Materials and Methods

Forty-two newly diagnosed leukemic children treated according to the ALL-BFM-90 schedule (prednisone 60 mg/m^2 days 1-29; *E. coli* L-asparaginase [Kyowa Hakko Kyogo, Japan] 10,000 U/m^2 days 12, 15, 18, 21, 24, 27, 30, 33; vincristine 1.5 mg/m^2 and daunorubicin 30 mg/m^2 days 8, 15, 22, 29) were evaluated over a 36-month period for this study.

Prophylactic single-donor FFP substitutions were administered when fibrinogen levels decreased to <60 mg/dL (recommendation: ALL-BFM 90) and thrombin time was lengthened (>28 sec). Single-donor FFP was individually tailored; necessary volume restrictions were taken into consideration, and the leukemic children received median doses of 10 (range 5-20) mL/kg each. For ethical reasons no randomization was performed. In addition, a non concurrent control group of 39 non substituted patients treated according to the same schedule is shown.

Correspondence: Ulrike Nowak-Göttl, Westfälische Wilhelms-Universität, Department of Pediatrics, Pediatric Hematology and Oncology, Albert-Schweitzer Str. 33, Tel. international +49.251.837783 Fax: international +49.51.837828, D-48149 Münster, Germany.
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Table 1. Median (range concentrations of fibrinogen, antithrombin, plasminogen and α_2-antiplasmin before, 1-3 h, 18 h and 48 h after substition with fresh frozen plasma in 20 leukemic children. In addition, a non concurrent control group of 39 substituted patients treated according to the same ALL-BFM 90 schedule is shown.

Parameter	*before*	*1-3h*	*18h*	*48h*	*control*
Fibrinogen mg/dL	42 (24-119)	45 (21-146)	50 (32-140)	52 (28-132)	64 (35-157)
Antithrombin %	62 (34-108)	62 (28-124)	60 (33-120)	58 (30-110)	59 (38-116)
Plasminogen %	45 (20-100)	48 (25-94)	45 (23-74)	37 (21-79)	53 (33-92)
α_2-antiplasmin %	52 (35-82)	52 (32-75)	48 (26-74)	61 (33-75)	52 (35-93)

Blood samples for coagulation studies were obtained before the first FFP substitution and 1-3 hours, 18 hours, and 48 hours after FFP administration.

TT was measured with an ILTest™ (Thrombin, Instrumentation Laboratory, Italy). Fibrinogen reagent kits purchased from Behring Werke (Marburg, Germany) were used for the Clauss method. Antithrombin, plasminogen and α_2-antiplasmin were measured with chromogenic substrates S 2765 and S 2251 (Chromogenix, Mölndal, Sweden); prothrombin fragment F 1+2, D-dimer and PAP were assessed with Enzygnost® F1+2 micro, EIA-D-dimer micro and Enzygnost® PAP micro (Behring Werke, Marburg, Germany).

Nonparametric statistical analyses were performed according to Wilcoxon and Spearman.

Results

Twenty children with ALL received 42 FFP doses after the 4th or 5th ASP administration, respectively. Laboratory monitoring before (n=20), 1-3 hours (n=12), 18 hours (n=20), and 48 hours (n=18) after FFP substitution demonstrated a minimal increase in fibrinogen (1 h: p=0.06; 18 h: p=0.03; 48h: p=0.07) and α_2-antiplasmin (48 h: p=0.05). Antithrombin and plasminogen remained unchanged (Table 1). Patients were substituted a median of three times (range 1-5). Figure 1 shows the course of fibrinogen and antithrombin single plasma values in leukemic children receiving more than one FFP substitution; no clinically important changes were found. Furthermore, administration of FFP had no influence on thrombin gen-

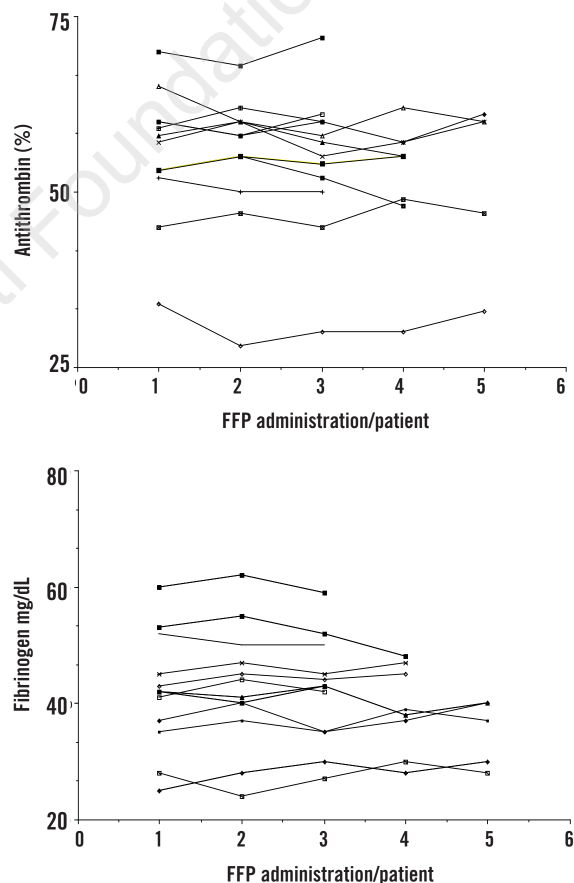

Figure 1. Course of single plasma values of antithrombin an fibrinogen before the first, second, third, fourth and fifth fresh frozen plasma administrations in leukemic children receiving more than one unit of FFP. While fibrinogen concentrations showed a minimal yet clinically unimportant increase, plasma levels of antithrombin remained unchanged during FFP administration.

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eration, the plasmin/α_2 antiplasmin complex or enhanced D-dimer formation. No bleeding complications occurred in these patients.

Discussion

In the present study single-donor FFP had no clinically relevant effect on ASP-induced coagulation activation, and no short-term improvement in the plasma levels of decreased coagulation proteins associated with bleeding tendency was found.

Despite the risk of viral transmission, children with acquired coagulation factor deficiencies secondary to a variety of disorders are frequently treated with FFP.[9] Depending on the quality of the FFP preparation administered, a median individual dose of 10 mL/kg bw normally causes a rise in clotting factors of about 15 to 20%.[10] Recently, in a prospective study Halton *et al.*[9] described the use of 20 mL/kg FFP in leukemic children treated according to the Dana-Faber Cancer Institute. This approach resulted in a very poor recovery of hemostatic proteins; as in our study, no significant effect was observed on enhanced D-dimer formation.

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