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Parenteral Nutrition Facilitates Activation of Coagulation but Not of Fibrinolysis during Human Endotoxemia

Tom van der Poll, Arnel Levi, Carla C. Braxton, Susette Coyle, arc Roth, Jan W. ten Cate, and Stephen F. Lowry

Venous thrombosis and bacterial infections are common complications of parenteral nutrition. To test the hypothesis that infection facilitates activation of coagulation during parenteral nutrition, healthy subjects were intravenously injected with endotoxin (2 ng/kg) after they had received either 1 week of standard parenteral nutrition (n = 7) or normal enteral feeding (n = 8). Compared with enteral feeding, parenteral nutrition was associated with a selectively enhanced activation of the coagulation system (plasma levels of thrombin-antithrombin III complexes) during endotoxemia. Activation of the fibrinolytic system (plasminogen activator activity, tissue-type plasminogen activator, plasminogen activator inhibitor type 1) proceeded similarly in both study groups. In patients receiving parenteral nutrition, one common complication (bacterial infection) may facilitate the occurrence of another common complication (venous thrombosis) by synergistic stimulation of the coagulation system.

Thrombosis of large central veins is a frequent, some times life-threatening complication in patients receiving parenteral nutrition. Clinical manifestations of venous thrombosis may occur in 10%–20% of patients receiving parenteral nutrition, whereas 40%–70% of patients had subclinical thrombosis during parenteral nutrition. Venous thrombosis may be caused by heparin-induced thrombocytopenia, coagulation disorders, or external compression. In a recent report, major thrombotic events, including pulmonary emboli, right atrial thrombi, and venous superior vena cava thrombosis, were found in 35% of children receiving long-term parenteral nutrition (n = 4). Several local factors have been implicated in the pathogenesis of thrombosis, such as hypercoagulability due to the presence of heparin in the central veins, including the composition of the central venous catheter material and the subsequent fibrin deposition. On the surface of the catheter, turbulence caused by the central venous catheter may induce thrombus formation.

Bacterial infec ions are known to cause venous osteoclu s (he coagulation system), and parenteral nutrition has been shown to enhance thrombogenesis by inducing procoagulant activity in heparin on endothelial cells and monocytes. This led us to hypothesize that bacterial infection may promote the occurrence of thrombosis and infec tions during parenteral nutrition. To test this hypothesis, we intravenously injected a low dose of endotoxin on the 9th day of the study (n = 7), followed by an additional dose on the 9th day (n = 7). This led us to hypothesize that bacterial infection may promote the occurrence of thrombosis and infections during parenteral nutrition.

Materials and methods

Study design. Fifteen male subjects (mean age ± SE, 28 ± 1 year) were admitted to the Adul Clinical Research Center of the New York Hospital–Cornell University Medical Center after receiving either normal enteral feeding or parenteral feeding for 1 week before endotoxin administration. The volunteers were divided into two groups: one group received endotoxin (2 ng/kg) after receiving normal enteral feeding, and the other group received endotoxin after receiving parenteral nutrition.

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The study was approved by the institutional Review Board of Cornell University Medical College and written informed consent was obtained from all subjects before enrollment in the study. Financial support: NIH (GM-34695, GM-08466, and RR-00047); Royal Netherlands Academy of Arts and Sciences (fellowship to T.v.d.P.).

Reprint requests or correspondence (premise affilliation): Dr. Stephen F. Lowry, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Dept. of Surgery, One Rober Wood Johnson Place—CN19, New Brunswick, NJ 08903-0019.

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or local irri a ion a he ca he er si e. Blood was ob ained before
and 1, 1.5, 2, 3, 4, 5, 6, and 24 h af er adminis ra ion of endo oxin.
Blood was also ob ained from paren erally fed volun eers before
he ini iaion of paren eral nu ri ion and 3 days hereaf er. All blood
samples were cen rifuged a 4°C for 20 min a 1600 g and s ored
a –70°C un il assayed.

A ssays. All assays were done in ci ra ed plasma samples. Co-
agula ion ac i a ion was de ermined by measuring hrombin-an i-
hrombin III (TAT) complexes (ELISA; Behringwerke, Marburg,
Germany). Fibrinoly ic ac i a ion was moni ored by measuremen s
of issue ype plasminogen ac i or ( PA) by use of an ELISA,
of plasminogen ac i or inhibit or ype 1 (PAI-1) by use of an
ELISA modified from an RIA, and of plasminogen ac i or ac iv-
i y by use of an amidoly ic assay. All assays have been described
in de ail previously [10, 11].

S tatistical analysis. All values are given as means ± SE. Com-
parisons wi hin and be ween groups were done by analysis of
variance followed by Newman-Keuls es for mul iple comparison
where appropria e. P<.05 was considered a as i cally signifi-
can difference.

R esults

Adminis ra ion of endo oxin o en erally fed subj c s resul ed
in a ransien ac i a ion of he coagula ion sys em, as reflec ed
by an increase in he plasma concen ra ions of TAT complexes
peaking af er 4 h (34.9 ± 4.0 ng/mL, P < .001) (figure 1).
Paren eral nu ri ion per se did no influence he plasma levels
of TAT complexes in he week prior o endo oxin adminis ra-
ion (da a no shown). However, paren erally fed volun eers
showed a significan ly more pronounced ac i a ion of he coag-
ula ion sys em af er endo oxin injec ion, wi h levels of TAT
complexes reaching a peak of 59.9 ± 3.8 ng/mL (P < .001
vs. en erally fed subj c s).

Injec ion of endo oxin was associa ed wi h ac i a ion of he
fibrinoly ic sys em, as indica ed by increases in he plasma
concen ra ions of plasminogen ac i or ac i y, PA, and PAI-
1 (all P < .001 vs. baseline) (figure 2). Paren eral nu ri ion
per se did no influence fibrinolysis indexes in plasma in he
week before endotoxin administration. Further, aci va ion of he fibrinolytic system during endotoxemia was not influenced by an exogenous parenenal nutrient ion, compared with enderal feeding (figure 2).

Discussion

Cerebral venous thrombosis and bacterial infec tive endocarditis are the most frequent complications of parenteral nutrition in patients. We hypothesized that bacterial infec tive endocarditis was more common among parentally fed people because of enhanced procoagulant response to endotoxin. Lowry et al. [15] reported that this response was modified by the metabolic response to endotoxin in humans. Ann Surg 1989;146:115–9.

Wolfe et al. [16] investigated the human model of low-grade endotoxemia as a paradigm for bacterial infec tive endocarditis, a model previously shown to induce aci va ion of bovine coagulant and fibrinolysis [11–13]. Al though parenteral nutrient ion did not influence serial plasma indices for aci va ion of he coagulant system and fibrinolytic system in humans, it may influence the onset of coagulant activation during sepsis [7–9].

Levi et al. [14] evaluated the relationship between heparin and fibrinolytic activation during endotoxemia. The prothrombin time was shortened after endotoxin administration, aci va ion of he coagulant system and fibrinolytic activity remained similar among orally or parenteraly fed subjects. Hence, the effect of parenteral nutrient ion did enhance endotoxin-induced coagulant activity [14]. Of import ance, the fibrinolytic activity remained similar in orally or parenteraly fed subjects (figure 2). However, the fibrinolytic activity declined after endotoxin administration, aci va ion of the coagulant system and fibrinolytic activity remained similar among orally or parenteraly fed subjects. Hence, the effect of parenteral nutrient ion did enhance endotoxin-induced coagulant activity at the same level of endotoxemia as a paradigm for bacterial infec tive endocarditis, a model previously shown to induce aci va ion of bovine coagulant and fibrinolysis [11–13].

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11. Levi M, en Ca e H, Bauer KA, e al. Inhibi ion of endoex induced aci va ion of coagula ion and fibrinolysis by pen orifline or by a monoclonal an i-issue fac or, a media or cri cal for fibrin ca ions of parenenal nutrient ion. Hence, the ne effec of parenenal nutrient ion was an enhanced endoex induced fibrin activity during endotoxemia. The prothrombin time was shortened after endotoxin administration, aci va ion of he coagulant system and fibrinolytic activity remained similar among orally or parenteraly fed subjects. Hence, the effect of parenteral nutrient ion did enhance endotoxin-induced coagulant activity at the same level of endotoxemia as a paradigm for bacterial infec tive endocarditis, a model previously shown to induce aci va ion of bovine coagulant and fibrinolysis [11–13].


