Parenteral nutrition facilitates activation of coagulation but not of fibrinolysis during human endotoxemia
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Published in:
The Journal of Infectious Diseases

DOI:
10.1086/517811

Citation for published version (APA):
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.
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 ia ion of paren eral nu ri tion and 3 days hereaf er. All blood samples were cen rifuged at 4°C for 20 min a 1600 g and s ored a −70°C un il assayed.

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

Statistical 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 s a is cally signifi- can difference.

Results

Adminis ra ion of endo oxin o en erally fed subjec s resul ed in a ransien ac iva 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- tion (da a no shown). However, paren erally fed volun eers showed a significan ly more pronounced ac iva ion of he coagula 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 subjec s).

Injec ion of endo oxin was associa ed wi h ac iva ion of he fibrinoly ic sys em, as indica ed by increases in he plasma concen ra ions of plasminogen ac iva or ac iv- 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

Figure 1. Ac iva ion of coagula ion. Mean (±SE) plasma concen- ra ions of hrombin-an i hrombin III (TAT) complexes af er in ravenous injec ion of endo oxin (2 ng/kg) a t = 0 in heal hy humans who had received o al paren eral nu ri ion (TPN, n = 7) or normal en eral feeding (EN, n = 8) in week before endo oxin adminis ra ion. * P < .05 vs. en erally fed humans by analysis of variance and Newman-Keuls es.

Figure 2. Ac iva ion of fibrinolysis. Mean (±SE) plasma concen- ra ions of plasminogen ac iva or (PA) ac iv- i y, issue ype plasmino- gen ac iva or (PA), and plasminogen ac iva or inhibi or ype 1 (PAI-1) af er in ravenous injec ion of endo oxin (2 ng/kg) a t = 0 in heal hy humans who had received o al paren eral nu ri ion (TPN, n = 7) or normal en eral feeding (n = 8, EN, closed circles) in week before endo oxin adminis ra ion.
week before endotoxin administration (data not shown). Further, ac i va ion of he fibrinolytic system during endotoxemia was not influenced by an e cced parental nutrition, compared with e neral feeding (figure 2).

Discussion

Cen ral venous hrombosis and bacular infeccon are he most frequent complicaons of parental nutrition. We hypothesized ha bacular infeccon during parental nutrition might result in synergic coagulation ac i va on ac i va on via a combina on e f c of bac teria and parental nutrition and the high levels of endotoxin circulating in the bloodstream. In our study, we utilized the human model of low-grade endotoxemia as a paradigm for bacular infeccon, a model previously shown to induce ac i va on of b ac terial coagulation and fibrinolysis (11–13). Although parental nutrition did not influence serum plasma indices for ac i va on of he coagulation system and fibrinolysis over 1 week, an ec ced parental nutrition led to enhanced endotoxin-induced coagulation ac i va on. Of import ance, he fibrinolytic response remained similar among orally or parenerally fed subjects. Hence, he e f c of pareneral nutrition on he fibrinolysis of parental nutrition was an enhanced tendency toward fibrinogenesis during endotoxemia. The pro hrombotic effect was further reac e by he hac e several hours after endotoxin administration, ac i va on of coagulation would proceed, while fibrinolysis was comple on off. We consider it unlikely ha he presence of an in venous ca he er, ra her han a 7-day period of bowel res, caused he enhancement of endotoxin-induced coagulation ac i va on. Indeed, it has been documented ha prolonged bowel res has an amplifying effect on he memory and systemic response to endotoxin, leading to enhanced ac u phase pro e produc ion, increased c our erregula ory hormone, splanchnic cy okine release, and increased neurephol ac i va on (14, 15). In accordance, ac i va on of endotoxin was associa ed in pa ien s with e exaggerated ac u phase pro e produc ion compared with he response in e rall y fed pa ien s (15). Our results add ha these previously published data a ha bowel res is associa ed with he enhanced procoagulant response of endotoxin.

In the present study, lipids were not u ilized as a component of he parental nutrition regimen. Since we recently demon strated has ra ed ha infusion of lipid emulsion in o endotoxemic volunteers also selec ively po en ia es coagulation ac i va on, we ha hou influencing fibrinolysis (13), he shift toward thrombogenesis may be even more pronounced in pa ien s on parental nutrition with lipids. We propose ha in pa ien s with bacular infeccon receiving parental nutrition and he fibrinogenetic system may change in response to he occurrence of venous hrombosis. These findings may have relevance for he selec ion of pa ien s with parental nutrition who are likely to bene ci from heparin prophylaxis.

References

5. Di Cos anzo J, Sas re B, Choux R, Kasparian M. Mechanism of hrombo ic s a e was fur her reac e by he ha several hours after endotoxin administration, ac i va on of coagulation was ill proceeded, while fibrinolysis was comple on off. We consider it unlikely ha he presence of an in venous ca he er, ra her han a 7-day period of bowel res, caused he enhancement of endotoxin-induced coagulation ac i va on. Indeed, it has been documented ha prolonged bowel res has an amplifying effect on he memory and systemic response to endotoxin, leading to enhanced ac u phase pro e produc ion, increased c our erregula ory hormone, splanchnic cy okine release, and increased neurephol ac i va on (14, 15). In accordance, ac i va on of endotoxin was associa ed in pa ien s with e exaggerated ac u phase pro e produc ion compared with he response in e rall y fed pa ien s (15). Our results add ha these previously published data a ha bowel res is associa ed with he enhanced procoagulant response of endotoxin. In the present study, lipids were not u ilized as a component of he parental nutrition regimen. Since we recently demon strated has ra ed ha infusion of lipid emulsion in o endotoxemic volunteers also selec ively po en ia es coagulation ac i va on, we ha hou influencing fibrinolysis (13), he shift toward thrombogenesis may be even more pronounced in pa ien s on parental nutrition with lipids. We propose ha in pa ien s with bacular infeccon receiving parental nutrition and he fibrinogenetic system may change in response to he occurrence of venous hrombosis. These findings may have relevance for he selec ion of pa ien s with parental nutrition who are likely to bene ci from heparin prophylaxis.

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