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Resuscitation of Endotheliopathy and Bleeding in Thoracic Aortic Dissections: The VIPER-OCTA Randomized Clinical Pilot Trial

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BACKGROUND: Thoracic aorta dissection is an acute critical condition associated with shock-induced endotheliopathy, coagulopathy, massive bleeding, and significant morbidity and mortality. Our aim was to compare the effect of coagulation support with solvent/detergent-treated pooled plasma (OctaplasLG) versus standard fresh frozen plasma (FFP) on glycocalyx and endothelial injury, bleeding, and transfusion requirements.

METHODS: Investigator-initiated, single-center, blinded, randomized clinical pilot trial of adult patients undergoing emergency surgery for thoracic aorta dissection. Patients were randomized to receive OctaplasLG or standard FFP as coagulation factor replacement related to bleeding. The primary outcome was glycocalyx and endothelial injury. Other outcomes included bleeding, transfusions and prohemostatics at 24 hours, organ failure, length of stay in the intensive care unit and in the hospital, safety, and mortality at 30 and 90 days.

RESULTS: Fifty-seven patients were included to obtain 44 evaluable on the primary outcome. The OctaplasLG group displayed significantly reduced damage to the endothelial glycocalyx (syndecan-1) and reduced endothelial tight junction injury (sVE-cadherin) compared to standard FFP. In the OctaplasLG group compared to the standard FFP, days on ventilator (1 day [interquartile range, 0–1] vs 2 days [1–3]; $P = .013$), bleeding during surgery (2150 [1600–3087] vs 2750 [2130–6875]; $P = .046$), 24-hour total transfusion and platelet transfusion volume (3975 mL [2640–6828 mL] vs 6220 mL [4210–10,245 mL]; $P = .040$, and 1400 mL [1050–2625 mL] vs 2450 mL [1400–3500 mL]; $P = .027$), and goal-directed use of prohemostatics (7/23 [30.4%] vs 13/21 [61.9%]; $P = .036$) were all significantly lower. Among the 57 patients randomized, 30-day mortality was 20.7% (6/29) in the OctaplasLG group and 25% (7/28) in the standard FFP group ($P = .760$). No safety concern was raised.

CONCLUSIONS: In this randomized, clinical pilot trial of patients undergoing emergency surgery for thoracic aorta dissections, we found that OctaplasLG reduced glycocalyx and endothelial injury, reduced bleeding, transfusions, use of prohemostatics, and time on ventilator after surgery compared to standard FFP. An adequately powered multicenter trial is warranted to confirm the clinical importance of the findings. (Anesth Analg 2018;127:920–7)

KEY POINTS

- **Question:** Is administration of solvent/detergent-treated pooled plasma (OctaplasLG) superior to standard fresh frozen plasma in patients undergoing acute surgery for thoracic aortic dissection?
- **Findings:** In this randomized trial of 44 critically ill patients, glycocalyx and endothelium injury, bleeding, transfusions, use of prohemostatics, and time on ventilators were significantly reduced.
- **Meaning:** OctaplasLG reduced glycocalyx and endothelial injury, and further improved hemostatic efficacy reducing bleeding during surgery compared to standard fresh frozen plasma.

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Conflicts of Interest: See Disclosures at the end of the article.

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The trial was registered before patient enrollment at clinicaltrials.gov (NCT02253082, principal investigator: J.S.; date of registration: October 1, 2014).

Reprints will not be available from the authors.

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Thoracic aortic dissection (TAD) is an acute critical condition with increasing incidence, carrying a high risk of significant morbidity and mortality.[1–3] In treated patients, a 30-day mortality of 15%–25% and organ failures, such as acute lung injury (ALI), continues to be a challenge.[2,4] Severe endothelial dysfunction and capillary leakage are pivotally involved in the high risk of morbidity and mortality.[5,6]

The endothelium is coated with a "thick" endothelial glycocalyx protecting it from activation by the coagulation system and preventing capillary leakage.[7,8] The glycocalyx comprises approximately 1 L of the plasma volume and regulates the dynamic exchange of molecules and fluids between the intravascular/extravascular space functioning as a barrier.[7] In 2007, Rehm et al[5] reported that global ischemia in patients undergoing aortic surgery on cardiopulmonary bypass (CPB) resulted in endothelial glycocalyx shedding. Degradation of the glycocalyx increases endothelial permeability with edema formation and ensuing risk of development of ALI, multiple organ failure, and death in TAD patients[9,10] but also in patients with myocardial infarction, out-of-hospital cardiac arrest, trauma, and sepsis,[11–15] suggesting a unifying pathophysiological mechanism, which we entitle shock-induced endotheliopathy (SHINE).[6] Hence, TAD patients operated in deep hypothermic circulatory arrest are prone to develop SHINE and capillary leakage for which no therapy has proven successful.[6]

In TAD-operated patients, massive transfusion with the use of plasma as coagulation factor replacement related to bleeding is most often a prerequisite.[4] In animal hemorrhagic shock models, administration of plasma, compared to crystalloids, is associated with improved endothelial integrity and restoration of the glycocalyx layer.[16–19]

OctaplasLG (Octapharma USA, Inc, Hoboken, NJ) is a pharmaceutically licensed (solvent/detergent-treated) plasma product pooled from approximately 1000 single donations. It possesses unique features such as more standardization in concentrations of natural procoagulation and anticoagulation factors related to the pooling process compared to standard fresh frozen plasma (FFP).[20–24] Importantly, OctaplasLG® is free of cells and debris due to several steps of microfiltration, of which one is a dedicated cell filtration (1 μm) step, during manufacturing, in addition to inactivation of viruses, and the removal of bacteria, parasites, and prion proteins.[25,26]

The investigator-initiated, Vasculopathic Injury and Plasma as Endothelial Rescue–OCTAplasLG (VIPER-OCTA) Randomized Clinical Pilot Trial aims to compare the effect of coagulation support with OctaplasLG versus standard FFP on endothelial and glycocalyx injury, bleeding, and transfusion requirements in patients undergoing emergency TAD surgery. We hypothesized that the administration of OctaplasLG would be superior to standard FFP in protecting against glycocalyx and endothelial injury and its downstream clinical effects, and further preserving hemostatic efficacy.

METHODS

Ethical Approval and Trial Conduct

This trial was approved by the Regional Committee on Health Research Ethics (ID H-3-2014-018), and written informed consent was obtained from all subjects. Patients were only enrolled after informed consent, but because the enrolled patients were temporarily incapacitated, they were all included after proxy consent by 2 independent physicians (a legal surrogate) according to Danish legislation. In all patients, informed consent was obtained from next of kin, if available, and the patient's general practitioner. In patients who regained consciousness, informed consent was obtained from all subjects as soon as possible. The trial was approved by the Danish Data Protection Agency and The Danish Medicines Agency (EudraCT no. 2014-000452-28). The trial was registered before patient enrollment at clinicaltrials.gov (NCT02253082; Principal investigator: J.S.; date of registration: October 1, 2014).

Trial monitoring was performed by the Good Clinical Practice Unit of Bispebjerg Hospital, Copenhagen University Hospital, according to the International Council for Harmonization guidelines. A dedicated team of data managers assessed data quality throughout the study, and the electronic trial database was generated and validated by independent double data entry. This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Design and Patients

We performed the first trial on endothelial rescue as an investigator-initiated, single-center, blinded, randomized, clinical pilot trial of patients admitted to Rigshospitalet, Copenhagen University Hospital, Denmark, undergoing emergency surgery for TAD randomized to administration of OctaplasLG or standard FFP as coagulation factor replacement related to bleeding.

We included all consecutive adult patients (≥18 years of age) eligible for emergency surgery on CPB for TAD Stanford type A (DeBakey classification type I involving the ascending aorta, aortic arch, and descending aorta, and type II confined to the ascending aorta) identified by computed tomography.

We excluded patients refusing blood transfusion; patients having received FFP transfusion before randomization; aortic dissection due to trauma; patients treated with glycoprotein IIb/IIIa inhibitors within 24 hours from screening; patients not expected to survive 24 hours or for whom therapy was withdrawn; patients previously (within 30 days) included in a randomized trial; and patients with known immunoglobulin A deficiency with documented antibodies against immunoglobulin A. Furthermore, we excluded patients with known hypersensitivity to OctaplasLG, known severe deficiencies of protein S and with confirmed pregnancy on arrival. For further details, please see Trial Registration—clinicaltrials.gov Identifier: NCT02253082. Surgery was performed as a standard in deep hypothermic circulatory arrest.

Study Outcome Measures

The primary outcome measure was glycocalyx and endothelial injury as measured by plasma levels of endothelial-derived biomarkers (syndecan-1, soluble thrombomodulin [sTM], soluble (s) E-selectin, sVE-cadherin) at 24 hours after surgery compared to the baseline defined as 15 minutes before weaning from CPB. These markers have been validated by us and are associated with mortality and outcome in different patient populations with acute critical illness.[6,16–20] Secondary outcome measures evaluated the

endothelial markers at 48 hours postoperatively compared to baseline, plasma biomarkers reflecting disease severity including inflammation and sympathoadrenal activation (C-reactive protein, interleukin-6 [IL-6], and catecholamines), bleeding during surgery and 24 hours after surgery, transfusion and prohemostatic requirements at 24 hours, renal failure defined by acute kidney injury according to Risk, Injury, and Failure; and Loss; and End-stage kidney disease criteria[27] and need for renal replacement therapy, and organ failure according to the Sepsis-Related Organ Failure Assessment score[28] in the first 7 postoperative days in the intensive care unit (ICU). Morbidity was further evaluated by the length of stay (LOS) in the ICU (LOS-ICU) and in the hospital, and mortality at 30 and 90 days. For evaluation of safety, we followed severe adverse reactions, transfusion-associated ALI, and transfusion-associated cardiac overload in the first 30 days.

Post hoc, we investigated the economic impact of the 2 treatment modalities on the cost of total transfusions of red blood cell (RBC) ($134 per unit), plasma ($88) and platelet concentrates ($268), LOS in ICU ($3490 per day), and LOS in hospital ($823).

Randomization and Blinding

Blood Bank research staff performed onsite randomization by envelope opening. The randomization was done in a block size of 6; sequence and envelopes were generated and validated by 2 independent people otherwise not involved in the trial. Randomization was performed using Microsoft Excel software (Microsoft, Redmond, WA), according to Altman and Bland.[29] Clinical staff caring for the patients in the transfusion phase were aware of the allocation, but the laboratory staff performing the biomarkers analyses and the statistician were blinded to the allocation.

Biomarker Measurements

Soluble biomarkers were measured by commercially available immunoassays in ethylenediaminetetraacetic acid (EDTA) plasma according to manufacturer recommendations: adrenaline and noradrenaline (2-CAT ELISA; Labor Diagnostica Nord GmbH & Co, KG, Nordhorn, Germany), syndecan-1 (Diaclone Nordic BioSite, Copenhagen, Denmark), sTM (Nordic BioSite), sE-selectin (IBL International GmbH, Hamburg, Germany), sVE-cadherin (R&D Systems, Inc, Minneapolis, MN), C-reactive protein, and IL-6.

Statistical Methods

Statistical analyses were performed by a statistician blinded to the allocation before breaking the randomization code. Mortality was reported as intention-to-treat (ITT) analysis including all randomized patients. Patients being evaluable on the primary end point were included in the further masked per-protocol (PP) analyses of the primary, secondary, and safety outcome measures, and an abstract was written before unblinding of the allocation.

Mortality was analyzed by χ^2/Fisher exact test; biomarkers were evaluated by delta values, relative values, and absolute differences at 24 and 48 hours (Mann-Whitney *U* test). Delta values were calculated as the absolute change from baseline to 24 or 48 hours, reported as, for example, nanogram per milliliter depending on the biomarker. Relative values were calculated as the proportional change from baseline (100%) to 24 or 48 hours, reported as percentage. Absolute differences were the difference between groups in "raw" values at 24 and 48 hours, reported as, for example, nanogram per milliliter depending on the biomarker. Continuous data were analyzed by Mann-Whitney *U* test and a mixed repeated model from days 0 to 7 (proc mixed SAS) with ante(1) covariance structure and Tukey post hoc tests, log-transformed if required based on AIC/AICC/BIC values. The factors in the model were treatment group, time and treatment group × time (interaction). The ante(1) covariance structure was chosen because this allows unequal space between measurements and because the variance among observations changes over time and depends on distance in time. Dichotomous data were analyzed by χ^2/Fisher exact test each time point or as an overall maximum or minimum value. Baseline balance was assessed in baseline parameters by Mann-Whitney *U* test or χ^2/Fisher exact test as appropriate. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

The investigators developed the trial design, protocol, and ensured trial execution, data analysis, and interpretation, writing, and submission of the paper. Investigators had full access to all of the data in the trial and take responsibility for the integrity and the accuracy of the data analysis.

Sample Size Estimation

The sample size calculation was based in part by data collected in a quality control investigation with the use of the endothelial marker sTM in OctaplasLG-treated TAD patients. The absolute value of sTM after surgery in FFP-treated patients was mean 3.35 ng/mL (standard deviation [SD], 2.12), and in OctaplasLG patients mean 1.70 (SD, 0.49), with SD across the entire group of patients: 1.574. To detect a mean difference of 1.5 ng/mL with a power of 0.90 ($1 - \beta$) and α of .05, n = 21 patients were required in each group. In the present trial, we choose to include 42 patients, 21 evaluable patients in each group in case of attrition.

RESULTS

Study Population

From November 2014 to July 2016, 57 subjects (ITT population) were randomized to obtain 44 evaluable patients with 21 patients in each group, as defined by having a measurement on the primary end point available at 24 hours postoperatively. Thirteen patients were nonevaluable on the primary outcome measure, 6 of 29 in the OctaplasLG group and 7 of 28 in the standard FFP group, leaving 44 patients available for analysis (PP population): 23 in the OctaplasLG group and 21 in the standard FFP group (Figure 1). No patients or relatives withdrew consent in the trial.

The groups were not statistically different in terms of demographic and other clinical characteristics (Table 1 and Supplemental Digital Content 1, Table 1S, http://links.lww.com/AA/C441).

Mortality

In the ITT population, 10 of 57 patients did not survive 24 hours: 4 of 29 (13.8%) in the OctaplasLG and 6 of 28

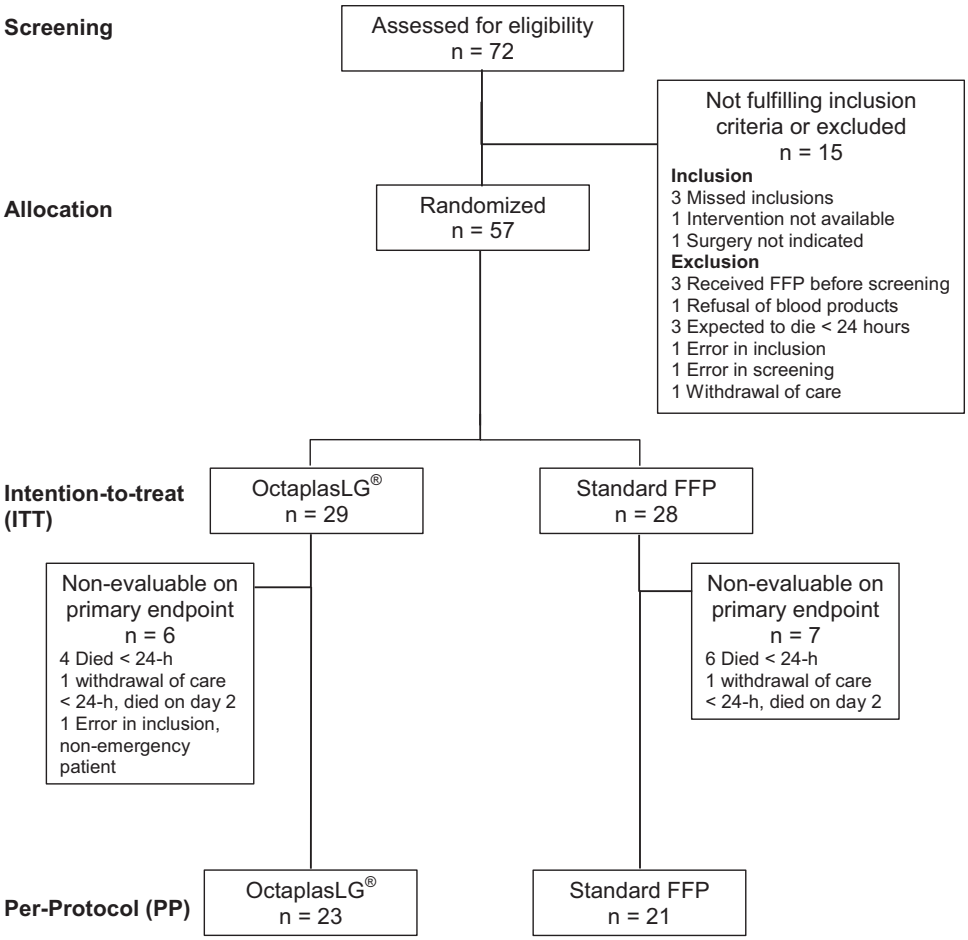

Figure 1. Study flow chart. FFP indicates fresh frozen plasma; ITT, intention-to-treat; PP, per-protocol.

(21.4%) in the standard FFP group (P = .505). One patient in each group developed severe brain injury within 24 hours causing withdrawal of therapy and fatality on day 2. One patient in the OctaplasLG group died within 30 days, leaving a 30-day mortality in this ITT population of 6 of 29 (20.7%) in the OctaplasLG group and 7 of 28 (25.0%) in the standard FFP group (P = .760). In the PP population, 30-day and 90-day mortality was 1 of 23 (4.3%) in the OctaplasLG group and 0 of 21 (0.0%) in the standard FFP group (P = 1.0).

Biomarkers of Endotheliopathy

The primary end point of glycocalyx and endothelial injury as measured by endothelial-derived biomarkers at 24 hours showed significantly reduced glycocalyx damage in the OctaplasLG group compared to standard FFP (further reduction in syndecan-1 in the OctaplasLG group compared with standard FFP; Figure 2A, Supplemental Digital Content 1–2, Table 1S, http://links.lww.com/AA/C441, Figure 1SA, http://links.lww.com/AA/C442) and a trend toward reduced endothelial cell tight junction injury in the OctaplasLG group (diminished increase in sVE-cadherin; Figure 2B and Figure 1SB). At 48 hours, a similar response, with a trend toward reduced glycocalyx damage (further reduction in syndecan-1; Figure 2A and Figure 1SA) and significantly reduced endothelial tight junction injury (diminished increase in sVE-cadherin; Figure 2B and Figure 1SB), was observed in the OctaplasLG group.

In relation to other measured biomarkers and timings (Supplemental Digital Content 1 and 3, Figure 2S, http://links.lww.com/AA/C441, Table 2S, http://links.lww.com/AA/C443), there was a decline in IL-6 from baseline to 24 hours only in the standard FFP group and higher IL-6 levels at 24 hours in OctaplasLG patients.

Bleeding, Transfusion Requirements, Prohemostatics, Organ Failure, and Severity of Morbidity

The intraoperative bleeding was significantly lower in the OctaplasLG group (median, 2150 mL [interquartile range, 1600–3087 mL] vs 2750 mL [2130–6875 mL]; P = .046) (Table 2). The total transfusion volume (RBC, plasma, platelet concentrates) in the first 24 hours was significantly lower in the OctaplasLG group (3975 mL [2640–6828 mL] vs 6220 mL [4210–10,245 mL]; P = .040). Especially, the volume of platelet concentrates transfused was significantly reduced in the OctaplasLG group (1400 mL [1050–2625 mL] vs 2450 mL [1400–3500 mL]; P = .027). Goal-directed use of prohemostatics was significantly lower in the OctaplasLG group (7 of 23 [30.4%] vs 13 of 21 [61.9%]; P = .036). On initiation of surgery on CPB, 9 of 23 (39.1%) in the OctaplasLG group and 8 of 21 (38.1%) in the standard FFP were receiving

≥1 antithrombotics (P = .95). More specifically, 3 of 23 (13%) vs 2 of 21 (9.5%) were on ticagrelor (P = .72), 2 of 23 (8.7%) vs 1 of 21 (4.8%) were on prasugrel (P = .5), 1 of 23 (4.3%) vs 1 of 21 (3.8%) were on clopidogrel (P = .95), 8 of 23 (34.8%) vs 8 of 21 (38.1%) were on aspirin (P = .82), 3 of 23 (13%) vs 2 of 21 (9.5%) were on fondaparinux (P = .55), and 2 of 23 (8.7%) vs 1 of 21 (4.8%) were on unfractionated heparin (P = .5) before initiating surgery on CPB.

Days on ventilator were lower in the OctaplasLG group 1 (0–1) day vs 2 (1–3) days in the standard FFP group (P = .013). The proportion on mechanical ventilation was significantly reduced on day 4, and there was a trend for the same on days 2–3 in the OctaplasLG group. In accordance with this, there was a trend toward improved oxygenation as measured by an improved Pao_2/Fio_2 ratio in OctaplasLG patients on days 3 and 4 (Supplemental Digital Content 1, Table 3S, http://links.lww.com/AA/C441).

Table 1. Demography

	OctaplasLG, Median (IQR)	Standard FFP, Median (IQR)
n	23	21
Age, y	60 (50–69)	60 (54–65)
Gender, male, n (%)	20 (87)	12 (57.1)
Weight, kg	89 (80–95)	80 (72–92)
Comorbidity		
ASA score	4 (4–4)	4 (4–5)
Diabetes, type 1, n (%)	0 (0)	0 (0)
Diabetes, type 2, n (%)	1 (4.3)	1 (4.8)
Ischemic heart disease, n (%)	2 (8.7)	0 (0)
NYHA classification score	I (I–I)	I (I–I)
Kidney failure, n (%)	0 (0)	0 (0)
Ischemic stroke, n (%)	1 (4.3)	0 (0)
Vascular disease, n (%)	2 (8.7)	0 (0)
Surgery		
CPB time, min	195 (170–238)	216 (195–250)
Isolated aortic replacement, n (%)	13 (56.5)	7 (33.3)
Aortic replacement with aortic valve repair, n (%)	9 (39.1)	12 (57.1)
Surgery involving the carotids, n (%)	1 (4.3)	3 (14.3)
Surgery involving a coronary vein graft, n (%)	2 (8.7)	3 (14.3)

All patients had aortic replacement performed.

Data are presented as medians (IQR) or n (%).

An ASA physical status classification score of 1 equates to no disease; 2, mild diseases; 3, severe diseases; and 4, severe disease that is a constant threat to life.

Abbreviations: ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IQR, interquartile range; NYHA, New York Heart Association.

Health Economy

The total costs for blood products transfused were significantly lower in the OctaplasLG group ($3114 vs $4913; P = .039). There was no significant difference between groups with regard to costs for ICU-LOS and LOS ($50,577 in the OctaplasLG group versus $65,355 in the standard FFP group; P = .470) or combined costs for blood products, LOS, and ICU-LOS ($53,691 vs $70,2678; P = .420).

Safety

No significant difference between the groups with regard to any safety measure was observed (Supplemental Digital Content 1, Table 4S, http://links.lww.com/AA/C441).

DISCUSSION

The main finding of this investigator-initiated, randomized, clinical pilot trial of patients undergoing emergency surgery for TAD was that OctaplasLG reduced damage to the endothelial glycocalyx at 24 hours and reduced tight junction injury at 48 hours compared to standard FFP. Also, OctaplasLG reduced intraoperative bleeding, total transfusion and prohemostatic requirements in the first 24 hours, and time on ventilators compared to standard FFP.

Systemic endothelial glycocalyx damage is a hallmark of global ischemia and reperfusion injury in TAD patients[5] as part of the SHINE pathophysiology.[6] This is confirmed in the present trial of TAD patients, demonstrating increasing levels of syndecan-1 from start of CPB until before CPB weaning (data not shown). Notably, the increased levels of syndecan-1 declined in both groups during the phase of hemostatic resuscitation with plasma, though the decline was significantly more pronounced in the OctaplasLG group indicating superior restoration of the glycocalyx.

The mechanism behind the apparently more protective effect of OctaplasLG is presently unclear, but it may be associated with the reduced amount of danger-associated molecular patterns, residual blood cells and cell fragments, microparticles, and cytokines in the solvent/detergent-treated and microfiltered pooled plasma product

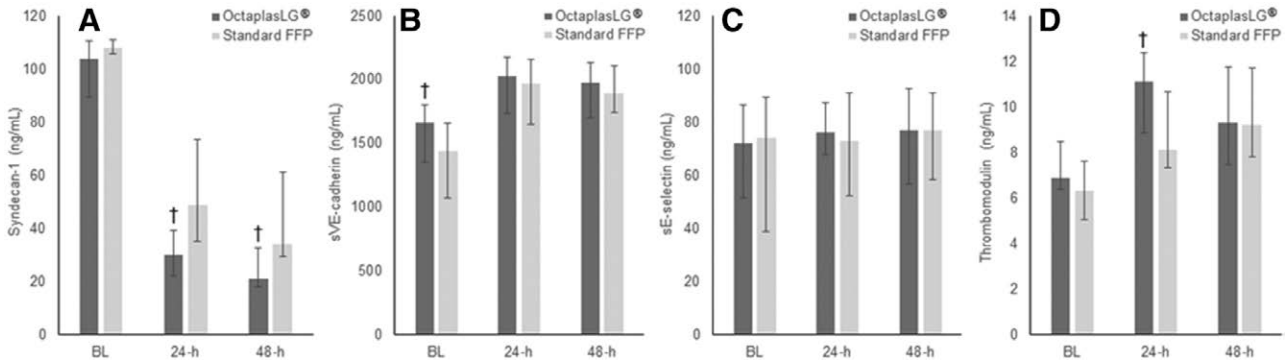

Figure 2. The absolute values of the endothelial-derived biomarkers are displayed: (A) syndecan-1, (B) sVE-cadherin, (C) sE-selectin, and (D) thrombomodulin at BL (ie, 15 min before weaning from cardiopulmonary bypass pump, 24 and 48 h after surgery in patients randomized to OctaplasLG or standard FFP). According to the primary end points, the relative changes at BL, at 24 h, and at 48 h in each group are compared by Mann-Whitney U test: †P < .05 and ‡P < .10. BL indicates baseline; FFP, fresh frozen plasma.

Table 2. Bleeding, Transfusion Requirements, Organ Failures, and Length of Stay

	OctaplasLG Median (IQR) (n = 23)	Standard FFP Median (IQR) (n = 21)	*P* Value
Bleeding, mL			
Intraoperative	2150 (1600–3087)	2750 (2130–6875)	**.046**
24-h postoperative	950 (500–1310)	1150 (713–3930)	.176
Transfusions from 0 to 24 h			
Red blood cells, n	5 (3–9)	7 (3–13)	.278
Red blood cells, mL	1225 (613–2205)	1715 (735–3185)	.305
Plasma, n	8 (5–10)	8 (6–14)	.292
Plasma, mL	1600 (900–2000)	2160 (1620–3780)	**.005**
Platelet concentrates, n	4 (3–8)	7 (4–10)	**.027**
Platelet concentrates, mL	1400 (1050–2625)	2450 (1400–3500)	**.027**
Total blood products, n	15 (11–26)	22 (15–35)	.142
Total blood products, mL	3975 (2640–6828)	6220 (4210–10,245)	**.040**
Goal-directed use of prohemostatics in the first 24 h			
Received fibrinogen concentrate, prothrombin complex concentrate, recombinant factor VIIa, or cryoprecipitate, n (%)	7 (30.4)	13 (61.9)	**.036**
Received fibrinogen concentrate, n (%)	7 (30.4)	12 (57.1)	.127
Received prothrombin complex concentrate, n	0	0	1.0
Received recombinant factor VIIa, n (%)	0	5 (23.8)	**.019**
Cryoprecipitate, n (%)	0	2 (9.5)	.222
Organ failure assessment			
Time on ventilators, d	1 (0–1)	2 (1–3)	**.013**
Mechanical ventilation needed, n (%)			
Arrival ICU	23 (100)	21 (100)	
Day 1	16 (69.6)	19 (90.5)	.137
Day 2	4 (17.4)	10 (47.6)	.052
Day 3	3 (13)	7 (33.3)	.052
Day 4	1 (4.3)	6 (28.6)	**.042**
Day 5	1 (4.3)	2 (9.5)	.599
Day 6	1 (4.3)	2 (9.5)	.599
Day 7	1 (4.3)	3 (14.3)	.345
Highest SOFA score days 0–7	8 (6–9)	8 (7–9)	.642
Highest AKI (RIFLE) score	1 (0–2)	1 (0–2)	.509
days 0–7			
Length of stay (LOS), d			
Hospital LOS	14 (10–37)	20 (14–44)	.165
Intensive care unit LOS	4 (3–7)	6 (3–11)	.102

Data are presented as medians (IQR) or n (%). The OctaplasLG and standard FFP groups are compared by Mann-Whitney *U* test or by χ^2/Fisher exact test as appropriate, with *P* values <.05 displayed in bold.

Abbreviations: AKI (RIFLE), acute kidney injury according to the Risk, Injury, and Failure; and Loss; and End-stage kidney disease criteria; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SOFA, Sepsis-Related Organ Failure Assessment.

(ie, reducing the injurious "hit" on the endothelium and surface compared to standard FFP). It is well established that nucleosomes, including histone-complexed DNA, are potent damage-associated molecular patterns,[30] and it has been shown that this results in endothelial damage.[31] In alignment with this, we found that in trauma patients, high levels of histone-complexed DNA were significantly associated with increased levels of both syndecan-1 and sTM reflecting glycocalyx and endothelial cell damage.[32]

Also, for the first time, we found evidence for a superior protective function of OctaplasLG on endothelial cell tight junction proteins, measured by sVE-cadherin. This is pivotal, given that disruption of endothelial cell tight junctions results in capillary leakage, hypotension, increased tissue pressure, and impaired oxygen delivery to vital organs.[9,10] Given the critical involvement of capillary leakage in pulmonary pathology, the reduced endothelial tight junction injury together with enhanced glycocalyx protection and repair in the OctaplasLG group may explain the observed reduction in time on ventilators and in the need for mechanical ventilation on day 4, with a similar tendency on days 2 and 3 compared to patients receiving standard FFP.

This is the first randomized, clinical trial comparing the effect of OctaplasLG and standard FFP on hemostatic competence in massively bleeding patients. Importantly, patients receiving OctaplasLG had a significant 21% reduction in bleeding during surgery and a 35% reduction in total transfusion volume in the first 24 hours compared to the standard FFP group. Even more notably, the volume of platelet concentrates transfused was also reduced in the OctaplasLG group by more than 1 L (median). Apart from the obvious reduction in costs for blood products in the OctaplasLG group, which translated into significantly reduced overall cost for transfusions in the OctaplasLG group, reduced transfusion requirements also indicate improved hemostatic efficacy.[33]

Patients included in the present trial received a standardized transfusion protocol delivering blood products in the ratio 1:1:1 of RBCs, plasma, and platelets, receiving 2 g of tranexamic acid on start of and again on weaning of CPB,

and receiving further goal-directed therapy with prohemostatics and antifibrinolytics based on Thrombelastography (TEG; Haemonetics, Braintree, MA). analysis if bleeding persisted, equally protocolized, and standardized in both groups. This has previously been presented as the Copenhagen Concept.[34,35] The amount of bleeding and need for transfusions are in alignment with other recent publications.[36,37] The improved hemostatic efficacy observed in the OctaplasLG group is further supported by the reduced need for goal-directed therapy with the use of fibrinogen concentrate, prothrombin complex concentrate, recombinant factor VIIa, and cryoprecipitate according to TEG in the OctaplasLG group. This is most likely related to standardized levels of coagulation factors in the OctaplasLG, ensuring that adequate thrombin generation, pivotal for intact hemostasis.[38] Standard FFP has large variations in coagulation factor levels between units depending on the individual blood donor[39] and low levels of just 1 coagulation factor involved in thrombin generation will result in impaired clot strength and reduced hemostatic competence.[34]

Plasma IL-6 decreased in both groups during the initial 48 hours, although the decline during the initial 24 hours was evident only in the FFP standard group, leading to higher IL-6 levels in the OctaplasLG group over time. Although the IL-6 level in both groups (≈50–250 pg/mL) was higher than that in healthy individuals (≈0–12 pg/mL),[40] it was considerably below levels observed in, for example, systemic inflammatory response syndrome after open-heart surgery (≈6.000–15.000 pg/mL).[41] The finding of higher plasma IL-6 levels in the OctaplasLG group is not likely explained by higher levels in the OctaplasLG preparation because the IL-6 range in this plasma product is lower than that of standard FFP.[42] Given the overall clinically beneficial effects of OctaplasLG in the present study, it is tempting to speculate if the modestly increased IL-6 levels in OctaplasLG patients may potentially promote an anti-inflammatory response rather than a proinflammatory response.[43] This, however, warrants investigation in future studies.

Study Limitations

The present pilot study has several limitations. First, it was a pilot trial with a limited number of participants, which precludes it from delivering robust causality between the observed findings and the intervention investigated. A causal relationship between the selected biomarkers and endothelial injury cannot be inferred. Furthermore, this trial was not blinded in relation to the clinical setting, which potentially could influence the results. Also, being a single-center study limits the generalizability of the results presented. Furthermore, the costs presented here are potentially underestimated since direct costs only are included, which typically only reflect a limited proportion of the overall societal cost and potentially not comparable to other countries. Moreover, we chose to study 4 biomarker levels as the primary outcome increasing the risk of multiplicity of tests; however, in this exploratory pilot trial, this was not planned as part of the statistical analysis plan but should be considered in a confirmatory trial. Last, data on TEG and supplementary tranexamic acid were not planned as part of the statistical analysis plan but should be considered in a confirmatory trial.

CONCLUSIONS

In conclusion, this investigator-initiated, randomized, clinical pilot trial of patients undergoing emergency surgery for thoracic aorta dissections demonstrated that solvent/detergent-treated pooled plasma (OctaplasLG) reduced damage to the endothelial glycocalyx and tight junction proteins compared to standard FFP. Furthermore, time on ventilators was reduced in patients treated with OctaplasLG. Importantly, OctaplasLG improved hemostatic efficacy and reduced bleeding during surgery, total transfusion and platelet transfusion requirements in the first 24-hour requirements, and also need for prohemostatics compared to standard FFP. An adequately powered multicenter trial is warranted to confirm the clinical importance of these significant findings. ■

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