ORIGINAL ARTICLE

Thrombotic and hemorrhagic complications during visceral transplantation: risk factors, and association with intraoperative disseminated intravascular coagulation-like thromboelastographic qualities: a single-center retrospective study

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SUMMARY

This study describes the risk of thrombotic and hemorrhagic complications, both intraoperatively, and up to 1 month following visceral transplantation. Data from 48 adult visceral transplants performed between 2010 and 2017 were retrospectively studied [32 multivisceral (MVTx); 10 isolated intestine; six modified-MVTx]. Intraoperatively, intracardiac thrombosis (ICT)/pulmonary embolism (PE) occurred in 25%, 0% and 0% of MVTx, isolated intestine and modified MVTx, respectively, and was associated with 50% (4/8) mortality. Preoperative portal vein thrombosis (PVT) was a significant risk factor for ICT/PE ($P = 0.0073$). Thromboelastography resembling disseminated intravascular coagulation (DIC) (r time <4 mm combined with fibrinolysis or flat-line) was statistically associated with occurrence of ICT/PE ($P < 0.0001$). Compared to subgroup without ICT/PE, occurrence of ICT/PE was associated with an increased demand for all blood product components both overall, and each surgical stage. Hyperfibrinolysis (56%) was identified as cause of bleeding in MVTx. Incidence of postoperative thrombotic event at 1 month was 25%, 30% and 17% for MVTx, isolated intestine and modified MVTx, respectively. Incidence of postoperative bleeding complications at 1 month was 11%, 20% and 17% for MVTx, isolated intestine and modified MVTx. In conclusion, MVTx recipients with preoperative PVT are at an increased risk of developing intraoperative life-threatening ICT/PE events associated with DIC-like coagulopathy.

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Key words
bleeding, disseminated intravascular coagulation, intracardiac thrombosis, multivisceral transplant, pulmonary embolism, thromboelastography

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Introduction

Visceral transplantation includes the grafting of the small intestine, alone, or as part of a multivisceral organ block, with the liver (MVTx) or without the liver (modified MVTx) [1,2]. This complex procedure is the only long-term therapy for patients with intestinal failure, commonly due to venous or arterial visceral thrombosis, that eliminates their dependence on parental nutrition and attendant complications [1–3]. Additional indications for visceral transplantation include otherwise unresectable benign or low-grade malignant tumors, desmoid, and neuroendocrine tumors, with or without hepatic metastasis, in the absence of extra-abdominal disease [1–4]. Despite current advancements in survival, when MVTx is performed in patients with extensive portal mesenteric thrombosis (PVT), it remains a surgical challenge that carries high risk of bleeding [4]. Rutter *et al.*'s [5] study reported a 29% 1-year mortality in MVTx recipients, with on-table bleeding responsible for 14% of mortality, and that thrombosis was among the other causes of early mortality. Older studies have suggested that disseminated intravascular coagulation (DIC) during orthotopic liver transplantation (OLT) is rare [6–8]. Recent studies have observed that coexisting morbidities may serve as a trigger for the development of DIC-related hemorrhagic and thromboembolic events in OLT [9,10]. Unfortunately, incidence of thrombosis and hemorrhage in visceral transplantation remains unknown.

The purpose of this observational study was to fill in this gap and to identify risk factors for the development of thrombotic and hemorrhagic complications intraoperatively, and up to 1 month after visceral transplantation. Derived knowledge was then used to develop a practical intraoperative coagulation management algorithm in patients undergoing visceral transplants, which include the liver.

Method

Following IRB approval, data were extracted from all 48 adult (≥18 years old) visceral transplant medical records performed at University of Miami/Jackson Memorial Hospital from 2010 to 2017 (Fig. 1). We defined thrombotic events as (i) intraoperative diagnosis of intracardiac thrombosis (ICT) or pulmonary embolism (PE); (ii) postoperative diagnosis of upper or lower deep venous thrombosis (DVT) or PE during the 1st month following transplantation. Intraoperatively, using transesophageal echocardiography (TEE), diagnostic of ICT was made by the direct visualization of intracardiac clots. Criteria for clinical diagnostic of intraoperative PE were (i) acute onset of systemic hypotension with sudden increase in central venous pressure from baseline and (ii) echocardiographic evidence for pulmonary artery clots, elevated pulmonary arterial pressure, or acute right heart pressure overload (dilated right ventricle and atrium with emptied left ventricle). Postoperatively, DVT was diagnosed with ultrasonography of the extremities, while PE was diagnosed with contrast-computed tomography of the chest. Hypercoagulable state work-up tested for deficiency of protein S, C, or antithrombin III, and for the presence of lupus anticoagulant. Diffuse thrombosis of the portomesenteric system was diagnosed with triple-phase computerized tomography, or with magnetic resonance imaging with venous reconstruction. Pretransplant history of DVT/PE or superior mesenteric artery (SMA) thrombosis was extracted from the medical record. Long-term anticoagulation was administered pre- and/or post-transplant to patients who had thrombotic complications, unless history of bleeding. All recipients received DVT prophylaxis with mechanical compression stockings intraoperatively. Once platelet count was $>40 \times 10^3/\mu l$, sq heparin 5000 units every 8 h, plus aspirin 81 mg po were initiated postoperatively.

The anesthesia management protocol included administration of general anesthesia and placement of two arterial catheters (radials or radial and femoral) plus 1–2 large-bore central venous access line (12F and 9F, usually right or left internal jugular vein based on accessibility). TEE was used in all cases, while continuous cardiac output Swan-Ganz pulmonary artery catheters were used until 2013. Thromboelastography coagulation monitoring (TEG; Haemonetics®, Braintree, MA, USA) was made at baseline, just prior to, and 30 min after reperfusion. Additional TEG tests were performed based on the clinical scenario. Utilizing TEG, fibrinolysis was defined in the presence of ≥7.5% reduction in amplitude 30 min after maximal amplitude (LY30 ≥7.5%) (Haemonetics®, TEG manual). Coagulation index: $[(0.1227 \times \text{R time} + 0.0092 \times \text{K time} + 0.1655 \times \text{MA}) - 0.0241 \times \text{Alpha angle} - 5.022]$, which combines all pro-coagulant TEG variables, was calculated for patients who developed ICT (Haemonetics®, TEG manual). Heparin and epsilon aminocaproic acid (EACA) administration was at the discretion of the team. Intraoperative blood product administrations were extracted from the anesthesia record. Transfusion of packed red blood cells (pRBC), fresh frozen plasma (FFP), platelets (PLTS), or cryoprecipitate (CRYO) was

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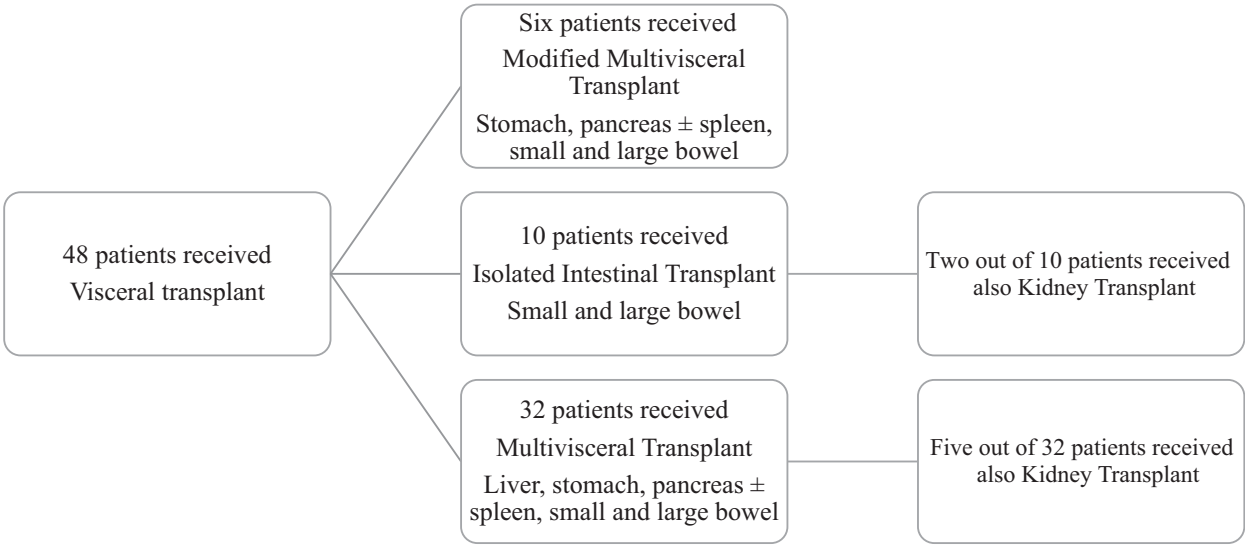

Figure 1 Visceral transplant flow chart.

based on blood loss and TEG analysis. In surgical situations with massive hemorrhage, using 1–2 rapid infusers (Belmont instrument Co., Billerica, MA, USA), an optimal FFP:pRBC ratio of at least 1:2 was given in mixture with normal saline. Transfusion of blood components aimed at restoration of hemostasis (TEG with R time 4–9 min; K time 1–3 min; alpha angle 59°–74°; maximum amplitude 55–74 mm). Thirty day postoperative hemorrhagic complications were defined as those necessitating exploratory laparotomy for control of bleeding.

After visual confirmation of excellent transplant quality, grafts were procured from deceased donors using standard harvesting techniques [3,4]. Organ matching was determined by blood type, donor medical history, and recipient size. The surgical technique included three stages: in stage I, the native organs were resected (visceral exenteration); stage II started with removal of the target organ(s) and consisted of the creation of arterial inflow and venous outflow anastomoses; stage III started with reperfusion of graft followed by reconstruction of gastrointestinal continuity and completion of the surgery. Veno–veno bypass was attempted in a single case (Patient#1; Table 2), but was aborted due to clotting of the *ex vivo* circuit.

Statistics

Categorical variables were presented as counts and percentages with differences between the groups assessed using chi-square (χ^2) tests. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Continuous variables with skewed distributions were presented as median and range (min–max) with differences between groups assessed by the Wilcoxon rank-sum test. Linear regression was performed between the three surgical stages and total pRBCs, FFP, PLTS and CRYO administered on patients with and without ICT to identify the relationship between the ICT and overall blood products administered. *P* values <0.05 signify statistical significance. All statistical analysis was performed using JMP PRO13 (SAS Institute, Cary, NC, USA).

Results

Demographic and pretransplant comorbidities are presented in Table 1. Preoperative screening for hypercoagulable state was available for 30 of 48 patients and showed reduced activity of antithrombin III (<80%) in 33% (10/30), protein S (<70%) in 53% (16/30), and protein C (<70%) in 40% (12/30) of the patients, while lupus anticoagulant was positive in 17% (6/36) of the patients. Two patients were diagnosed preoperatively with myeloproliferative syndrome (polycythemia vera) pretransplant. The overall incidence of any pretransplant thrombotic event (DVT, PE, SMA thrombosis or PVT) was 54% (26/48) with SMA thrombosis 15% (7/48), PVT 25% (12/48) and DVT/PE 31% (15/48). Half of the patients that presented with PVT had also history of DVT/PE. Pretransplant thromboprophylaxis done in 17% (8/48) of the patients included coumadin (one patient) or low-molecular-weight heparin (seven patients). Inferior vena cava filter was placed in two patients.

Table 1. Demographic and pretransplant comorbidities on patients receiving a visceral transplant.

	MVTx $n = 32$		Modified MVTx + isolated intestine $n = 16$		*P* value
Age, years	49 (18–68)		37 (18–62)		0.0346*
Male, *n*%	17 (53%)		5 (31%)		0.1516
MELD, medical	13 (6–32)		8 (6–14)		0.0009*
Caucasian, *n*%	22 (69%)		9 (56%)		0.4738
BMI	24 (17–38)		21 (17–31)		0.0272*
Redo-transplant, *n*%	4 (12.5%)		2 (12.5%)		0.6880
PVT, *n*%	12 (38%)		0		0.0047*
Previous abdominal surgery, *n*%	25 (78%)		15 (94%)		0.1709
TPN, *n*%	16 (50%)		15 (94%)		0.0028*
Pretransplant RRT, *n*%	6 (19%)		0		0.0215*
Pretransplant hospitalization, *n*%	7 (22%)		4 (25%)		0.8081
Systemic hypertension, *n*%	24 (75%)		12 (75%)		0.6306
Diabetes, *n*%	5 (16%)		2 (13%)		0.7724
CAD, *n*%	1 (3%)		0		0.4749
History of smoking, *n*%	7 (22%)		6 (38%)		0.2508
History of DVT/PE, *n*%	11 (19%)		4 (25%)		0.7422
Etiology	SGS/ESLD, *n*%†	15 (47%)	SGS, *n*%	11 (68%)	<0.0001*
	ESLD# extensive PVT, *n*%	8 (25%)	Gardner syndrome, *n*%	2 (13%)	
	SGS extensive PVT, *n*%	3 (9%)	Intestinal failure, *n*%	2 (13%)	
	Neuroendocrine tumor, *n*%	4 (13%)	Intestinal dysmotility, *n*%	1 (6%)	
	Gardner syndrome, *n*%	1 (3%)			
	Carcinoid tumor, *n*%	1 (3%)			

BMI, body mass index; CAD, coronary artery disease; DVT deep vein thrombosis; ESLD end-stage liver disease; MELD, model for end-stage liver disease; MVTx, multivisceral transplant; PE, pulmonary embolism; PVT, portal vein thrombosis; RRT, renal replacement therapy; SGS, short gut syndrome; TPN, total parenteral nutrition.

The values are presented as median (minimum and maximum) or as numbers (*n*) and percentages (%).

*$P < 0.05$ is statistically significant.

†One patient had partial PVT, One patient history of failed MVTx, ×2 and one patients history of failed intestinal transplant.

#Viral hepatitis (3); Alcohol (1); Autoimmune hepatitis (1); Cryptogenic (1) and liver failure secondary to a modified MVTx (1) and liver transplant (1).

Intraoperative thrombotic and hemorrhagic complications

The incidence of intraoperative ICT/PE was 25% (8/32), 0% (0/10), and 0% (0/6) for MVTx, isolated intestine, and modified MVTx, respectively ($\chi^2 = 7.2$, $P = 0.0265$). ICT/PE was associated with 50% (4/8) intraoperative mortality. Preoperative PVT was statistically associated with ICT/PE [OR 8 (1.512–40.806); $\chi^2 = 7.2$, $P = 0.0073$]. Characteristics of these eight patients and heparin treatment are shown in Table 2. ICT/PE occurred during stages II and III of surgery. Intracardiac clots were visualized initially in the right heart in six of eight patients; left heart involvement occurred later in three patients who died intraoperatively. After ICT/PE event resolved, EACA therapy was given to four of eight ICT/PE patients for severe generalized bleeding; patient #6 received EACA therapy for DIC pattern prior to two ICT events. In the MVTx group, cold ischemia time showed no statistical difference between patients with ICT/PE versus no ICT/PE: 510 (443–704) and 478 (282–680) min, respectively ($\chi^2 = 1.8$, $P = 0.1843$). There was no statistical difference in warm ischemia time between patients with ICT/PE versus no ICT/PE: 33 (20–45) and 28 (16–53) min, respectively ($\chi^2 = 1.4$, $P = 0.2395$).

The median blood transfusion was significantly higher for MVTx compared with modified MVTx/isolated intestine for all products [pRBC 22 (2–132) & 2 (0–14), $\chi^2 = 21$, $P < 0.0001$; FFP 13 (0–105) & 0 (0–9) $\chi^2 = 23$, $P < 0.0001$, PLTS 3 (0–26) & 0 (0–1) $\chi^2 = 16$, $P < 0.0001$; CRYO 1 (0–20) & 0 (0–1) $\chi^2 = 16$, $P < 0.0001$, respectively]. The analysis of blood component requirements in MVTx group ($n = 32$) is presented in Table 3. Compared to subgroup without ICT/PE, occurrence of ICT/PE was associated with an

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Table 2. Intraoperative thrombotic events: patient data and clinical characteristics for visceral transplant that include the liver (MVTx).

No	Age	Sex/race	Redo	Etiology	DVT /PE	Coagulation disorders	MELD	pRBC, units	DIC types TEG stages	Severe hypotension (mean <50 mmHg)/ massive bleeding/ Epinephrine	ICT intraoperative stages/ location	Heparin Dose/stages	EACA Dose/stages	Death
1	53	Male/Caucasian	No	ESLD alcohol/PVT	Yes	Polycythemia vera	27	78	DIC type B, C Stage I	Stage I	#VVBP clotted Stage II/right heart failure/ hemodynamic collapse/ increase CVP/CPR/left heart clot/CPB	#Yes/1000 units Yes/Stage II 40 000 units	None	Death intraoperative
2	55	Male/Caucasian	Yes	ESLD: liver transplant graft failure/PVT	Yes	Protein S deficiency	20	97	DIC type C Stage II	Stage II/III	Stage II right heart clot Stage III right heart failure/ hemodynamic collapse/left heart clot/CPR	1st No/Stage II 2nd Yes/Stage III 2000 units	None	Death intraoperative
3	68	Male/Afro American	No	ESLD: hepatitis B/PVT	No	Protein C deficiency	32	28	DIC type B Stage II	Stage II	Stage II/hemodynamic collapse/increase CVP/RV mild dysfunction	No	Stage III: 2.5 g	Death GVHD @ 0.2 years
4	53	Female/ Caucasian	Yes	SGS/ESLD: TPN failed small bowel transplant	No	Not tested	7	132	DIC type C Stage II/III	Stage II/III	Stage II/III right heart clot	No	Stage III: 1.5 g	Death intraoperative
5	57	Female/ Caucasian	No	SGS/ESLD: alcoholic	No	Normal	7	37	DIC type A Stage II	Stage II	Stage II/right heart clot	Yes/Stage II 2000 units	Stage III: 0.3 g	Death MSOF @ 1.8 years
6	60	Male/Caucasian	No	ESLD: hepatitis C/PVT	Yes	ATIII, protein C and S deficiency	27	118	DIC type A, B Stage I/II	Stage I/II/III	Stage III ×2/1st right heart clot 2nd right/left heart clot/ CPR	1st Yes/Stage III 3000 units 2nd Yes/Stage III 22 000 units	Stage II: 0.25 g Stage III: 0.3 g	Death intraoperative
7	46	Female/ Caucasian	No	SGS/ESLD: TPN	No	Protein S deficiency	11	44	DIC type A Stage III	Stage III	Stage III/right heart clot	No	None	Alive
8	60	Male/Caucasian	No	SGS/ESLD: cryptogenic/PVT	No	ATIII, protein C and S deficiency	13	58	DIC type B Stage III	Stage III	Stage III/right heart clot	Yes/Stage III 3000 units	Stage III: 5 g ×2 boluses followed by 1 g/h	Alive

ATIII, antithrombin III; CPB, cardiopulmonary by-pass; CPR, cardiopulmonary resuscitation; CVP: central venous pressure; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; EACA, epsilon-aminocaproic acid; ESLD, end-stage liver disease; GVHD, graft-versus-host disease; ICT, intracardiac thrombosis; MELD, model for end-stage liver; MSOF, multisystem organ failure; PE pulmonary embolism; disease; pRBC, packed red blood cells; PVT, portal vein thrombosis; SGS, short gut syndrome; TEG, thromboelastogram; TPN: total parenteral nutrition.

#Patient 1 had a tentative veno–veno bypass with failure because of clotting.

increase demand for all blood components; both overall (pRBC: $\chi^2 = 20$, $P < 0.0001$; FFP: $\chi^2 = 18$, $P < 0.0001$; PLTS: $\chi^2 = 11$, $P = 0.0009$; CRYO: $\chi^2 = 13$, $P = 0.0003$), and for each surgical stage, Table 3.

The incidence of postreperfusion fibrinolysis was 56% (18/32), 0% (0/10), and 0% (0/6) for MVTx, isolated intestine, and modified MVTx, respectively ($\chi^2 = 14.4$, $P = 0.0007$), with a median LY30 of 51% (8.6–81.8). Postreperfusion, EACA was administered in 28% (9/32) of the patients, with a median dose of 1.25 g (0.25–15). Occurrence of fibrinolysis was statistically associated with an increase in blood product requirement postreperfusion (pRBC: $\chi^2 = 28$, $P < 0.0001$; FFP: $\chi^2 = 29$, $P < 0.0001$; PLTS: $\chi^2 = 23$, $P < 0.0001$; CRYO: $\chi^2 = 25$, $P < 0.0001$).

Three distinct TEG patterns were observed in ICT/PE group, see Fig. 2. TEG displaying a short r time (<4 min), combined with fibrinolysis or flat-line TEG, in the absence of heparin, was statistically associated with ICT/PE ($\chi^2 = 42$, $P < 0.0001$). In ICT/PE group, a median coagulation index of 2.3 (1.4–5.3) was calculated, with median R time 2.9 min (2.5–3.9); K time 1.5 min (0.9–2.2); maximum amplitude 51 mm (5.3–70.6) and alpha angle 70° (21–77), LY30 17% (3.3–62.5).

Postoperative thrombotic and hemorrhagic complications

After exclusion of the four perioperative deaths, the overall incidence of postoperative venous thrombotic complications up to 1 month in all visceral transplant recipients was 25% (11/44); majority of which were upper extremity DVT 91% (10/11), followed by PE 9% (1/11). The incidence of postoperative thrombotic event at 1 month was 25% (7/28), 30% (3/10), and 17% (1/6) for MVTx, isolated intestine, and modified MVTx, respectively ($\chi^2 = 0.43$, $P = 0.8069$).

After exclusion of the four perioperative deaths, the overall incidence of postoperative bleeding complications in visceral transplant was 14% (6/44) with two major events secondary to aortic jump graft rupture and four events secondary to coagulopathy. The

Table 3. Blood products administration in multivisceral transplant patients ($n = 32$): with and without intraoperative thrombosis.

Intraoperative thrombosis YES $n = 8$	pRBCs (units)		FFP (units)		Platelets (units)		Cryoprecipitate (units)	
Overall	68 (28–132)		43 (5–105)		7 (0–26)		6 (1–20)	
Stage I	9 (3–25)		6 (0–25)		0 (0–2)		0 (0–2)	
Stage II	12 (1–34)		7 (1–24)		2 (0–3)		1 (0–5)	
Stage III	38 (24–113)		27 (12–90)		4 (0–24)		5 (0–19)	
Nonparametric	*Z* scores	*P* values	*Z* scores	*P* values	*Z* scores	*P* values	*Z* scores	*P* values
Stage III versus Stage I	3.212603	0.0013*	2.629395	0.0086*	2.919077	0.0035*	2.919077	0.0035*
Stage III versus Stage II	2.837654	0.0045*	2.944922	0.0032*	1.804025	0.0712	1.651055	0.0987
Stage II versus Stage I	0.421637	0.6733	0.000000	1.0000	2.663128	0.0077*	2.208705	0.0272*
Intraoperative thrombosis NO $n = 24$	pRBCs (units)		FFP (units)		Platelets (units)		Cryoprecipitate (units)	
Overall	11 (2–128)		7 (0–76)		2 (0–8)		1 (0–6)	
Stage I	2 (0–38)		0 (0–27)		0 (0–4)		0 (0–1)	
Stage II	4 (0–22)		2 (0–14)		0 (0–3)		0 (0–1)	
Stage III	5 (1–104)		5 (0–69)		1 (0–8)		1 (0–5)	
Nonparametric	*Z* scores	*P* values	*Z* scores	*P* values	*Z* scores	*P* values	*Z* scores	*P* values
Stage III versus Stage I	2.209405	0.0271*	3.009927	0.0026*	3.567722	0.0004*	4.014713	<.0001*
Stage III versus Stage II	1.287111	0.1981	2.542865	0.0110*	3.383031	0.0007*	3.738505	0.0002*
Stage II versus Stage I	1.114707	0.2650	0.706486	0.4799	0.408475	0.6829	0.565456	0.5718

FFP, fresh frozen plasma; pRBC, packed red blood cells.

The values are presented as median (minimum and maximum) or as numbers (n) and percentages (%).

*$P < 0.05$ is statistically significant.

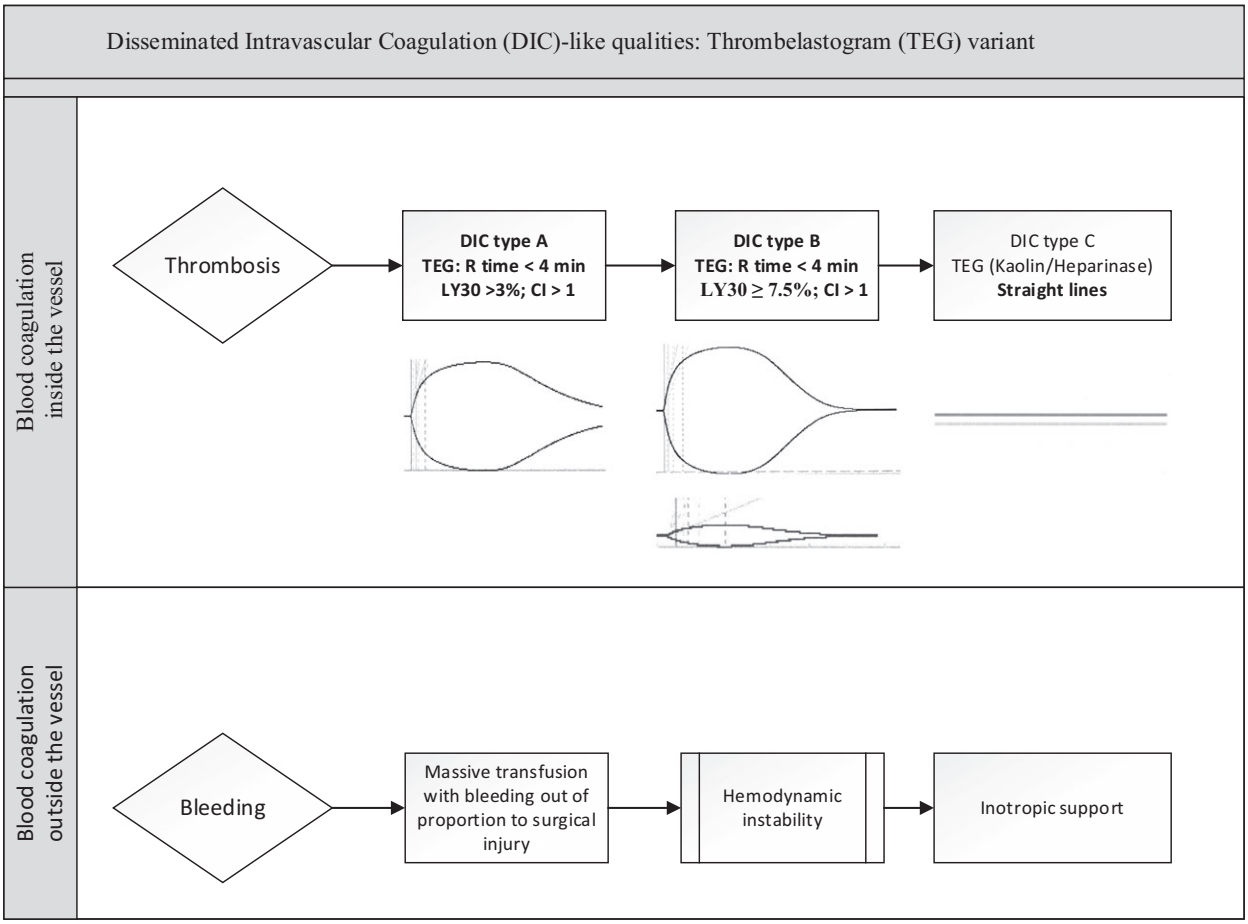

Figure 2 Disseminated intravascular coagulation-like qualities: thromboelastogram variant. CI, coagulation index; LY30 > 3%, TEG fibrinolysis >3% reduction in amplitude 30 min after maximal amplitude; LY30 ≥ 7.5%, TEG fibrinolysis ≥7.5% reduction in amplitude 30 min after maximal amplitude.

incidence of postoperative bleeding complications at 1 month was 11% (3/28), 20% (2/10), and 17% (1/6) for MVTx, isolated intestine, and modified MVTx, respectively ($\chi^2 = 0.59$, $P = 0.7432$).

Discussion

This study-striking incidence of 25% ICT/PE in MVTx is significantly higher than the reported range of 0.36–6.25% in patients undergoing OLT [9–11]. However, intraoperative cardiac thromboembolic events during OLT appear to be underreported, as a recent TEE study reported incidence of 27% [12]. Of note, no ICT/PE events were observed during isolated intestine, or modified MVTx in the current study. Multivisceral transplant entails many clinical factors that are associated with intraoperative ICT/PE, namely cirrhosis with its unsteady coagulation balance, extensive surgical dissection, potential for severe hemorrhage, and portomesenteric vein thrombosis in many recipients. Thus, from the clinical standpoint, it is not surprising when more ICT/PE events occur with MVTx than with OLT, isolated intestine transplant, or modified MVT. Another large center is reporting similar issues, as well, although without much details [5]. Routine use of TEE and heightened awareness for ICT/PE during haemodynamic instability and hemorrhage have likely enabled us to more precisely detect the occurrence of this complication.

Intraoperative and in-hospital mortality following ICT/PE event in the present study were 50% (4/8), and 63% (5/8), respectively. Multiple cardiac clots were seen in all patients with intraoperative mortality. ICT/PE was also found to be highly lethal complication in a systematic review of 74 OLTs, with overall, and intraoperative mortality rate of 68% and 55%, respectively [13]. A retrospective review of 495-OLT found 4% incidence of intraoperative PE, associated with intraoperative, and

in-hospital mortality of 30%, and 45%, respectively [14]. While extensive PVT was found to be a risk factor for morbidity and mortality in our study, Vianna *et al.* [4] reported no intraoperative thrombotic complications in 25 patients with grade IV portomesenteric thrombosis. Preoperative hypercoagulability was not tested in their study, nor was there routine usage of TEE; thus, ICT/PE was most likely missed or underdiagnosed.

Detection of ICT/PE with intraoperative TEE warrants immediate and adequate heparinization [14–17]. Spontaneous resolution of ICT/PE was observed with (patients #5&8) or without heparin administration (patients #3,4,7). Thrombolytic such as recombinant tissue plasminogen activator (tPA) 2–4 mg remains second-line therapy reserved for patients with large clots, especially when accompanied by cardiovascular instability [16–18]. None of our patients received tPA.

Hyperfibrinolysis (56%) was identified as pathological source of bleeding postreperfusion in MVTx. The safety of antifibrinolytics remains unclear, as they may trigger thrombosis, especially in the context of DIC [19]. Antifibrinolytics were a plausible cause for ICT in several reports [20,21]. Occurrence of two ICT events in Patient #6 shortly after less than 500 mg EACA administration, in the absence of pretreatment with heparin, strongly supports this notion. In contrast, Patient #8 received heparin pretreatment and had a rapid and uneventful resolution of DIC type B with a total dose of 15 g EACA. We currently treat fibrinolysis associated with DIC-like pattern on TEG with antifibrinolytics, only after effective pretreatment with heparin. Despite the efficacy of heparin in blocking extensive activation of coagulation in DIC [22], indications for its use vary significantly [19]. Based on the novel findings of this study and results from our previous studies [23,24], we developed and implemented a practical intraoperative coagulation management algorithm, see Fig. 3. The proposed algorithm aims at thrombosis prophylaxis combined with safe management of fibrinolysis-induced hemorrhage, if indicated, without triggering or worsening thrombosis. The proposed algorithm was not employed at any point during the study.

As our study reveals, PVT/cirrhosis is a primary risk factor for intraoperative thrombohemorrhagic DIC-like complications in MVTx, due to its unsteady pro- and anticoagulation balance, extensive dissection, and potential for severe hemorrhage. An additional means to minimize bleeding during MVTx that we recently employed is a pretransplant embolization of the superior mesenteric artery while preserving celiac trunk [25,26].

Concept of coagulopathy in DIC with simultaneous "intravascular thrombosis" and "extravascular exsanguinations" is illustrated in Fig. 2 [27]. Diffuse, severe hemorrhage, and haemodynamic instability, requiring massive transfusion and vasopressors, preceded each ICT/PE event in the present study. Others [9,14] reported similar observations in OLT. We characterized three distinct TEG patterns, types A, B and C, as stages

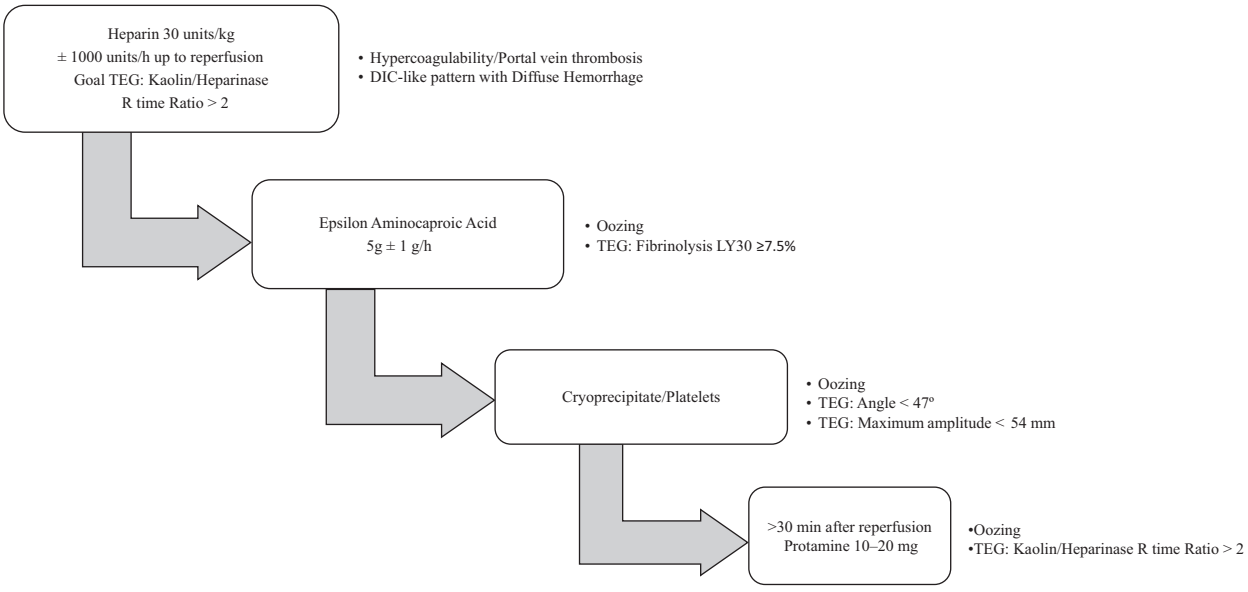

Figure 3 Coagulation management algorithm for multivisceral transplant. DIC, disseminated intravascular coagulation; LY30 ≥ 7.5%, TEG fibrinolysis ≥7.5% reduction in amplitude 30 min after maximal amplitude; TEG, thromboelastogram.

in thrombotic–hemorrhagic DIC-like condition, as those appear to be a predictor for development of ICT/PE in present study. Previous case reports support the association of DIC-like TEG pattern with hypercoagulability in OLT [9,14–16]. A flat line (type C) TEG may be erroneously attributed to hypocoagulability, while its *in vivo* counterpart is actually a full-blown, hypercoagulable DIC-like state with massive activation of fibrinolysis [14].

Preoperative screen for hypercoagulability was available in 63% of the patients and consistently included only some of the many conditions known to be associated with hypercoagulability. Of two patients diagnosed with myeloproliferative disorders, one died with intraoperative PE (Patient #1) and the other one had PE on day 12 post-transplant. Routine perioperative thromboprophylaxis was shown to effectively decrease thrombotic complications in patients with prothrombotic conditions in simultaneous kidney–pancreas transplant [28]. The high rate of pre- and post-transplant DVT/PE (31% and 25%, respectively), found in this study, suggests that postoperative thromboprophylaxis is warranted.

This report is the first case-series of thrombohemorrhagic complications observed in visceral transplants. The strength of this study is the continuous use of TEE and TEG monitoring by allowing early identification of thrombotic events and TEG patterns associated with those complications. The small number of patients and the retrospective nature of this single institution study is a limitation. Further studies are needed to accurately characterize the intraoperative thrombohemorrhagic DIC-like state.

In conclusion, MVTx recipients with pretransplant PVT appear to be at a higher risk of developing intraoperative life-threatening ICT/PE events associated with DIC-like coagulopathy. In patients with preoperative hypercoagulable risk factors, intra- and postoperative thromboprophylaxis with heparin are warranted, as the thrombotic risk outweighs the increased risk of bleeding.

Authorship

RY: designed research/study, analyzed data, and wrote the manuscript. RY: designed research/study, collected data, and wrote the manuscript. PE: designed research/study and wrote the manuscript. SF: designed research/study and wrote the manuscript. SV: designed research/study and wrote the manuscript. AB: designed research/study and wrote the manuscript. MV: designed research/study and wrote the manuscript. DM: designed research/study and wrote the manuscript. LJ: designed research/study and wrote the manuscript. NG: collected data. AD: wrote the manuscript. BT: designed research/study and wrote the manuscript. VR: designed research/study and wrote the manuscript. N-RR: collected data, analyzed data, and wrote the manuscript.

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Conflict of interest

The authors of this manuscript have no conflict of interests to disclose as described by the Transplant International.

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