

# Perioperative standards for the treatment of coagulation disorders and usage of blood products in patients undergoing liver transplantation used in the Clinic for Transplant Surgery in Wrocław

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D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online)

*Adv Clin Exp Med.* 2018;27(9):1211–1215

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## Funding sources

None declared

## Conflict of interest

None declared

Received on May 17, 2016

Reviewed on June 6, 2016

Accepted on March 9, 2017

## Abstract

**Background.** Coagulation system disorders in liver transplantation (ltx) patients are considered a serious issue. Liver cirrhosis leads to decreased synthesis of clotting factors and decreased elimination of waste products, including coagulation proteins. Platelet sequestration and dysfunction in an enlarged spleen additionally worsen these conditions. The resulting state, the most common pathology of the coagulation system, involves the reduction of clotting potential and hyperfibrinolysis.

**Objectives.** Tackling the problem of impaired hemostasis is a dynamic process. Throughout the whole procedure, consisting of the preanhepatic, the anhepatic and the neohepatic phases, consecutive pathomechanisms disrupt the very balance that anesthesia aims to preserve.

**Material and methods.** Rotational thromboelastometry (ROTEM), having been introduced in the Clinic of Anesthesiology and Intensive Therapy, Wrocław Medical University, Poland, enables the efficient and early diagnosis of clotting disorders. An additional major problem which occurs during ltx, namely blood loss, could be solved using a cell separator.

**Results.** In this study, we present the standards introduced to the Transplantology Department of the Vascular Surgery Clinic, Wrocław Medical University, Poland, that describe blood treatment during ltx procedures.

**Conclusions.** We conclude that thromboelastometric examination and the use of a cell separator have significantly increased the safety of ltx procedures at our clinic. The introduction of thromboelastometry (TEM) and the implementation of the cell separator recovery method have enabled us to perform the dangerous and complicated surgical procedure of ltx in a much more stable and much safer manner than in the past.

**Key words:** point of care, thromboelastometry, cell separator, liver transplantation

## DOI

10.17219/acem/69398

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## Introduction

Liver cirrhosis is a disease which leads to disruptions in the functioning of many organs and systems. Liver dysfunction leads to impaired metabolic and endocrine pathways in the body, causes disorders in blood coagulation, and impairs the cardiovascular, renal and pulmonary systems. In the coagulation system specifically, cirrhosis manifests itself through decreased synthesis and an impaired removal of functional proteins.<sup>1</sup>

The reduced synthesis of fibrinolytic inhibitors and a simultaneous extenuation of reticuloendothelial clearance leads to increased fibrinolysis, which is especially amplified in the anhepatic phase of liver transplantation (ltx). Portal hypertension and blood drainage through the spleen promote platelet sequestration and induce thrombocytopenia and an abnormal functioning of platelets.

During surgery, the abovementioned disorders are exacerbated by a loss of blood. Supplementation of blood with neutral fluids leads to dilutional coagulopathy. Heparinoids released during the neohepatic phase promote the activation of fibrinolysis. In addition to an increased risk of bleeding, inadequate treatment of coagulopathy in many cases leads to disseminated intravascular coagulation in the newly created vascular anastomoses and in the clamped inferior vena cava.<sup>1,2</sup>

## Objectives

The aim of perioperative therapy is to stabilize the clotting system as a safeguard against diathesis and bleeding as well as to prevent excessive clotting, especially in the vasculature of the newly transplanted liver.

Hemostasis for ltx patients consists of normothermia, a normal blood pH, a normal  $\text{Ca}^{2+}$  level, and normal blood count (recommended hemoglobin level: 8–10 g%).

The treatment of coagulation disorders is aimed at the creation of a balance between the pro- and anticoagulation systems. Homeostasis in the clotting system is often achieved when the coagulation parameters are below standard. Interference in an imbalanced system and excessive replacement of one of the clotting factors lead to further disruptions in the unstable balance and may eventually result in hemorrhagic diathesis or thrombosis.<sup>2–5</sup>

Dealing with the issue of impaired hemostasis is a dynamic process. Throughout the whole surgery, consisting of the pre-, an- and neohepatic phases, the resulting pathomechanisms disrupt the balance that anesthesia aims to preserve.

New hemostasis assessment methods: thromboelastometry (TEM), the concept of point-of-care, and the superiority of modern methods of coagulation system assessment over the previously used quantitative methods.

Point-of-care (POC) tests are performed near or bedside the patient. Traditionally these tests were performed in laboratory. Advanced technology enables quick obtainment of test results and rapid treatment decisions. The recent

concept of treating coagulation system disorders during the procedure of ltx is based on a dynamic assessment of the coagulation system through viscometry. The most commonly used method is rotary thromboelastometry (ROTEM).

The immediate availability of diagnostic results allows an appropriate therapy to be established and the effectiveness of therapeutic interventions to be evaluated.<sup>2,5–7</sup> Treatment of coagulation dysfunction via TEM also identifies the occurrence of hyperfibrinolysis, which is recognized as the cause of late bleedings.

Currently, we have 2 agents that inhibit the activity of plasminogen: epsilon-aminocaproic acid (EACA) and tranexamic acid (Exacyl®). It is very difficult to assess and diagnose hemostasis based solely on TEM, both in terms of the coagulation cascade and fibrinolysis.

Decisions about diagnosis and treatment should be based on the appearance or disappearance of parenchymal bleeding.

Surgery is evaluated as safe and proper according to the amount of blood lost from the surgical field. The concept of general anesthesia for ltx is based on creating hemodynamic conditions which minimize blood loss from the surgical field (low central venous pressure [CVP] anesthesia).

It is acknowledged that with an increasing amount of transfused blood, the likelihood of complications and side effects also increases. This significantly worsens the patients' prognosis.<sup>8,9</sup> In order to reduce the number of transfusions, extravasated blood is recovered from the operating field by a cell separator.

## Material and methods

The concept of prevention of intraoperative coagulation disorders is based on the assessment of the results of a coagulation system diagnosis, performed directly on the surgical patient in the operating room (POC).

Rotary thromboelastometry diagnosis based on POC provides the clinically relevant data necessary for the treatment of coagulation disorders as early as 10 min after obtaining measurements from the blood sample. Additionally, apart from standard laboratory tests, ROTEM evaluates fibrinolysis, coagulation dysfunction due to platelet disorders, and the influence of endogenous and exogenous heparinoids.

Thromboelastometry is performed in a fixed temporal and causal setting.

### Anesthesia standards for a liver transplantation patient

Surgical ltx is performed under typical anesthetic procedures, such as monitoring of the following parameters:

1. the depth of anesthesia (BIS monitoring – of the bispectral index);

2. skeletal muscle relaxation (neuromuscular transmission monitor – TOF Guard);
3. anesthetic gas concentrations in the respiratory mixture;

4. plethysmography.

Hemodynamic monitoring includes the following:

1. electrocardiography (ECG);
2. direct blood pressure measurement – the catheter is usually inserted into the radial artery;
3. CVP;
4. pulmonary artery pressure (the Swan-Ganz catheter) and hemodynamic tests performed with the thermodilution technique;
5. hourly diuresis monitoring;
6. core body temperature.

Vascular access includes peripheral cannulation established in the catchment area of the superior vena cava (upper limb), a central line access and a high flow catheter (minimum cross-section: 12 F) inserted through the internal jugular or the subclavian vein, and a vascular sheath (7.5–8 F) for introducing the Swan-Ganz catheter (7 F).

Blood is recovered from the operating field using a Dideco Electra cell separator (Sorin Group, Milan, Italy).

Anesthetics include Diprivan®, sufentanil, triacrium, and desflurane.

Substances can be administered in the form of standard, fractionated doses and continuous infusions: tranexamic acid, calcium chloratum, insulin, norepinephrine, vasopressin, epinephrine, and dobutamine.

Solutions of 0.9% NaCl, 20% glucose and human albumin are typically used, in addition to concentrated red blood cells (PRBC), platelet concentrate, blood coagulation factors, fresh frozen plasma (FFP), cryoprecipitate, fibrinogen, prothrombin complex concentrate, and factor VIIa.

The hemodynamic treatment of patients undergoing ltx complies with the standards of restrictive infusion therapy (low CVP anesthesia), yet does not differ from the standards of ensuring proper oxygen delivery to the tissues ( $\text{DO}_2$ ) and maintaining proper visceral flow and a urine output of at least 0.5 mL/kg/h.

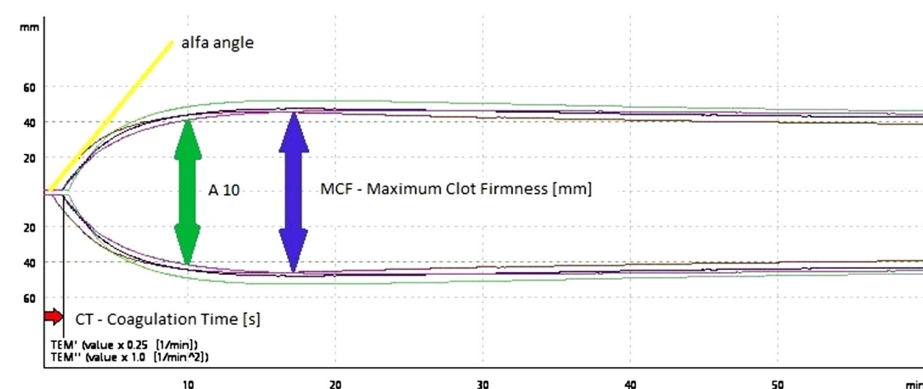
The treatment and maintenance of hemostasis are based on the results of TEM performed by a ROTEM delta device (Tem Innovations GmbH, Munich, Germany). This diagnostic method describes the process of coagulation in the whole blood (we get preliminary results 10 min after a blood sample) and enables fast therapeutic intervention. Decision-making about the treatment of coagulation disorders is always based on clinical observation and assessment is made by the operator.

Standard treatment of coagulation disorders applied in the Department of Vascular, General and Transplantation Surgery, Wrocław Medical University, Poland, is based on the Compendium of Recommendations from the Society of Essener Runde algorithm and European guidelines for the management of bleeding and coagulopathy.<sup>2,5,10</sup>

## Examination protocol

Standard measurements include the assessment of intrinsic and extrinsic clotting pathways by means of ROTEM (INTEM and EXTEM assays), the differentiating activity of fibrinogen and thrombocytes (FIBTEM assay), and the patients' response to anti-fibrinolytic treatment (APTEM assay).

The thromboelastometric graph shows time periods and amplitudes which correspond to the components of the coagulation cascade (section CT – coagulation time,  $\alpha$  – angle alpha, CFT – clot formation time, A – amplitude, MCF – maximum clot firmness, and CL – clot lysis) (Fig. 1).



EXTEM	EXTEM	EXTEM	EXTEM
PatientID:	PatientID:	PatientID:	PatientID:
SampleID:	SampleID:	SampleID:	SampleID:
Name: 1 pobranie godz. 10. 16.11.14	Name: preanhep 13.40 ( otrzymal 4 j FFP)	Name: 16.00 anhepatic anhepatic 16.00 otrzymal kolene 2 FFP	Name: neoheptic 17.32
CT : 44 s	CT : 109 s	CT : 86 s	CT : 82 s
CFT : 106 s	CFT : 79 s	CFT : 105 s	CFT : 120 s
$\alpha$ : 76 °	$\alpha$ : 76 °	$\alpha$ : 77 °	$\alpha$ : 71 °

Fig. 1. The example of thromboelastometric examinations (EXTEM) during phases of LTX

The first initial examination is performed immediately after the admission of the patient to the operation theatre. It provides an initial assessment of coagulation disorders and a reference to the implemented therapy. Further tests are carried out 60 min into the procedure, during the pre-anhepatic phase, at the early anhepatic phase, and at every 30 min of the neohepatic phase. Subsequently, they are also carried out 5–10 min after reperfusion and, finally, 30 min after the beginning of the neohepatic phase.<sup>2</sup> Standard tests (EXTEM, INTEM, FIBTEM, and APTTEM) are extended by the HAPTEM test in case of suspected heparin pollution of the blood cell separator (the fast track procedure in case of massive bleeding).

Additionally, after each intervention aimed at the correction of blood clotting, a treatment control test is performed. Clotting disorders reported by the surgeon, usually referred to as parenchymal bleeding, are handled in accordance with the recommendations of the Essener Runde algorithm for ROTEM. For example, parenchymal intraoperative bleeding requires the administration of fibrinogen when MCF (EX) <45 mm and MCF (FIB) <15 mm, the administration of platelets when MCV (EX) <45 mm and MCF (FIB) >15 mm, the substitution of prothrombin complex factors when CT (EXT) >80 s, and the substitution of FFP factors when CT (INT) >280 s. Anti-fibrinolytic treatment is managed using tranexamic acid when ML (EX) >15%, with an initial dose of 2 g (25 mg/kg) followed by a continuous infusion of 10 mg/kg/h and ROTEM tests.<sup>1</sup>

During surgery, the blood extravasated from the operating field is sucked out by a cell separator. After it proceeds through the phases of collecting, filtering and rinsing, a significant portion of the red blood cells is recovered (cell suspension in saline solution with hematocrit [Ht]

50–70%). The red blood cell suspension in saline solution is transfused to the patients' circulation immediately after each rinsing. The device estimates the amount of blood leakage, thereby making it possible to calculate the adequate amount of plasma needed to properly compensate for total blood loss. We maintain a standard hemoglobin level of 8–10 g/dL.

## Results

Since the introduction of viscometry based on POC as a clotting system diagnostic method in 2015–2016 and the standard for erythrocyte recovery from the surgical field using a blood cell separator, 12 orthoscopic ltx have been performed. The results are presented in Table 1.

The observations presented in the table show that the main factor of coagulation supplemented to ltx patients was fibrinogen. The dosages of fibrinogen were in the range of 3–10 g per procedure. Furthermore, all patients with confirmed hypofibrinogenemia were given Exacyl® as a standard measure in our department.

In our observations, in almost half of the patients undergoing ltx, the second-most supplemented substances were prothrombin complex factors and plasma, the latter mainly in the case of a deficiency in intrinsic path factors VIII, IX, XI, and XII, but not for a deficiency in prothrombin complex factors.

A cell separator was used in cases of suspected or increased blood loss, and was always ready for immediate use in case it was needed. As shown in the presented data, only 3 patients received an infusion for the blood lost from the surgical field, and there was no significant bleeding in the remaining cases.

**Table 1.** Intraoperative blood loss and the use of clotting factors during liver transplantation in the Department of Vascular, General and Transplantation Surgery, Wrocław Medical University, Poland, 6/26/2015–4/4/2016

No. of a patient	Date	Separator [mL]	Re-transfusion [mL]	FFP (u-unit)	PC	PRBC (u-unit)	Fibrinogen	Prothrombin-complex	Factor VIIa	Exacyl®	Cryoprecipitate
1	6/26/2015	low	–	–	–	–	3 g	1,500 u	–	2 g	–
2	8/27/2015	2,390	1,109	–	–	–	7 g	1,000 u	–	2 g	–
3	9/20/2015	low	–	–	–	–	4 g	–	–	2 g	–
4	10/1/2015	low	–	2 u	–	2 u	4 g	–	–	2 g	–
5	11/5/2015	low	–	2 u	–	2 u	2 g	–	–	2 g	–
6	11/13/2015	800	300	–	–	2 u	8 g	–	–	2 g	–
7	12/21/2015	1,000	169	–	–	–	6 g	2,000 u	–	2 g	–
8	1/8/2016	low	–	2 u	–	2 u	6 g	–	–	2 g	–
9	1/30/2016	low	–	–	–	–	10 g	2,000 u	–	2 g	–
10	2/19/2016	low	–	2 u	–	2 u	6 g	1,000 u	–	2 g	–
11	3/17/2016	2,845	974	2 u	–	1 u	6 g	–	–	2 g	–
12	4/4/2016	low	–	–	–	–	4 g	–	–	2 g	–

FFP – fresh frozen plasma; PC – platelet concentrates; PRBC – concentrated red blood cells; 1 unit PRBC = 250 mL; 1 unit FFP = 250–300 mL; low cell separator not in use, lack of excessive bleeding.

Patients 2 and 11 in Table 1 experienced significant bleeding (Patient #2: 2400 mL and Patient #11: 3000 mL). The use of a cell separator and the recovery of almost 1000 mL of red blood cell suspension enabled ltx to be performed without any blood transfusion whatsoever in the case of Patient #2, and using only 1 additional unit (250 mL) of PCRB to Patient #11. These results directly show a significant decrease in the quantity of foreign blood transfusions when using a cell separator.

## Conclusions

The concept of POC and the implementation of TEM are a generally acknowledged standard of modern ltx. The introduction of POC diagnostic standards and blood cell separators to common practice could – according to our team – reduces the number of blood transfusions and related complications, including transfusion-related acute lung injury (TRALI), infections and the immunization of the patient.

The use of TEM for the assessment of coagulation disorders allows the replenishment of selective deficiencies, restoring the balance of the coagulation system. This leads to a reduced number of previously, often only intuitively, prescribed transfusions of components such as plasma and platelets, simultaneously diminishing the risk of thrombotic embolism.

A very important achievement of applying these standards is the implementation of a coagulation system diagnostic method that quickly and conveniently describes the pathological mechanisms of coagulation observed in the surgical field and, at the same time, reflects the effectiveness of the implemented therapy or lack thereof.

Thanks to the standards introduced, we gained a quick diagnostic method that enables an appropriate choice of therapeutic strategy. As soon as 10 min after the beginning of the procedure and filling of the sample cuvettes, we are able to obtain preliminary results of the activation of the extrinsic and intrinsic coagulation cascade pathways and parameters evaluating the consolidation of the forming clot.

The introduction of TEM and the implementation of the cell separator recovery method have allowed us to perform the dangerous and complicated surgical procedure of ltx in a much more stable and much safer way than in the past.

## References

1. Møller S, Henriksen HJ, Bendtsen F. Extrahepatic complications to cirrhosis and portal hypertension: Haemodynamic and homeostatic aspects. *World J Gastroenterol.* 2014;20(42):15499–15517.
2. Görlinger K. Coagulation management during liver transplantation [in German]. *Hamostaseologie.* 2006;26(Suppl 1):64–75.
3. Hartog A, Mills G. Anaesthesia for hepatic resection surgery. *Continuing Education in Anaesthesia, Critical Care & Pain.* 2009;9(1):1–5.
4. Feltracco P, Brezzi ML, Barbieri S. Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. *World J Hepatol.* 2013;5(1):1–15.
5. Lier H, Vorweg M, Hanke A, Görlinger K. Thromboelastometry guided therapy of severe bleeding. Essener Runde Algorithm. *Hemostaseologie.* 2013;33(1):51–61.
6. Ganter MT, Hofer CK. Coagulation monitoring: Current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg.* 2008;106(5):1366–1375.
7. Krzanicki D, Sugavanam A, Mallett S. Intraoperative hypercoagulability during liver transplantation as demonstrated by thromboelastography. *Liver Transpl.* 2013;19(8):852–861.
8. Rouillet S, Pillot J, Freyburger G, et al. Rotation thromboelastometry detect thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. *Br J Anaesth.* 2010;104(4):422–428.
9. Romero FA, Razonable RR. Infections in liver recipients. *World J Hepatol.* 2011;3(4):83–92.
10. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: An updated European guideline. *Crit Care.* 2013;17(2):R76.