The novel hemostatic approach to perioperative treatment and nursing care in liver transplantations without the administration of blood products

Doctoral (PhD) Theses

Tímea Rengeiné Kiss

Semmelweis University
Doctoral School of Pathological Sciences

Supervisor: János Fazakas MD, PhD

Official reviewers: Andrea Székely MD, PhD
Gábor Nardai MD, PhD

Head of the Final Examination Committee:
Péter Sótonyi MD, member of the Hungarian Academy of Sciences

Members of the Final Examination Committee:
Antal Dezsőfi MD, PhD
Erika Erdősi MsC, PhD

Budapest
2020

1. Introduction

Hundreds of thousands of patients die of liver failure each year worldwide and over 5,000 patients do so in Hungary yearly. The only therapeutic option for patients with end-stage liver disease is liver transplantation.

The outcomes of liver transplantation show an improving tendency, which fact is also supported by the Kaplan-Meier curve indicating the average 5-year survival rate around 70–75%. Moreover, liver transplantation has become a life-saving procedure for patients, allowing more people to get transplantation as a life-saving therapy, while its indications are becoming more diverse. Modern anesthesia and hemostaseology along with the emerging novel microsurgical techniques play a pivotal role in the increase of the number of blood product-free liver transplants. The cell-based model and the "equilibrium" approach to hemostasis have become emphasized, while the range of techniques for bedside monitoring of hemostasis have been expanded and the administration of coagaulation factor concentrates has steadily increased. Thus, more differentiated therapeutic interventions have become feasible.

Intraoperative blood loss may be due to surgical bleeding or microvascular coagulopathy. The possible causes of surgical bleeding are adhesions, resulting fromprevious abdominal surgeries, or vascular factors due to portal hypertension. These conditions can lead to diffuse bleeding depending on hemostatic reserves.

Bloodless liver transplantation is a less invasive procedure with the benefits of shorter theatre and ICU stays. What is more, these patients will certainly not develop any transfusion-related complications such as transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and transfusion-related immunomodulation (TRIM). However, vigilant monitoring and nursing care is unquestionably crucial in these cases.

The aim of this research was to evaluate the kinteics of coagulation factors and the kinetics of hemostasis volume reserves in the first perioperative 48 hours after blood product free LTs and to explore what paradigm shift is necessary concerning the

allocation of human resources, nursing activities and care in liver transplant patients, due to the innovative development in hemostasis management.

2. Aim of the research

The aim of this research was to evaluate the perioperative kinetics of coagulation factors in blood product free LTs. We also aimed to examine the coagulation factor-specific volume reserves according to Child-Pugh score. In order to minimize the presence of any factors that may affect perioperative hemostasis, the research was considered worthwhile in the settings of liver transplants without the administration of any blood products or factor concentrates.

We also aimed to examine the perioperative nursing workload using a score system adapted for liver transplant recipients and to validate the worktime and nurse/patient ratio in accordance with clinical practice. We examined which nursing activities are required in an organ-specific approach in the first 48 hours.

2.1. Research phase I. Investigation of perioperative coagulation factor kinetics / Investigation of the perioperative kinetics of coagulation factors

Data from a number of bloodless liver transplants have been published, however, these reports neither did focus on the kinetics of perioperative coagulation factor levels nor on the inevitable decrease of coagualtion factor reserves.

Hypotheses:

- We assume to that the levels of blood coagulation factors significantly decrease during liver transplants, which losses are represented by the reduction of fibrinogen levels at least by 1 g/L and by the decrease of cogulation factors II, V, VII, X, XIII by more than 50%.
- We assume to that these aforementioned intraoperative losses in the coagulation factor levels are restored by the liver graft within 48 hours by its synthetic function Accordingly, the kinetics of the coagulation factors can be characterized by a tickmark-shaped curve.

2.2 Research phase II. Determination of perioperative hemostatic reserves

The principle of allowable blood loss has been applied for decades to determine hemoglobin limits for anemic hypoxia. Similarly, with the adaptation of the same principle for coagulaion factors, the loss of blood volume that puts the patient into the risk of diffuse bleeding and coagulopathy might be determined.

Hypotheses:

- We assume that the dynamic monitoring of coagulation factor specific volume reserves supplements the conventional and viscoelastic methods of hemostasis monitoring in the perioperative period of liver transplantation.
- We assume that the probability of blood product-free liver transplants could be estimated in an individual patient based on the evaluation of specific coagulation factor reserves. Consequently, the management of hemostasis can be tailored to the individual and an easier-to-plan and goal-directed perioperative treatment can be implemented.

2.3. Research phase III. Examination of the nursing workload and procedures

Perioperative care of liver transplant recipients requires complex therapeutic and nursing interventions, of which close multimodal monitoring and organ-specific supportive therapies are prominent.

Hypotheses:

- We assume that blood product-free liver transplantation involves less nursing workload. Since there is an absence of transfusion related complications, presumably a reduction in organ specific or therapeutic nursing activities might be observed as well
- We assume that blood product-free liver transplantation has a beneficial effect on the nurse/patient ratio in the early perioperative period of liver transplantation.

3. Methods

3.1. Research phase I. Investigation of perioperative coagulation factor kinetics

3.1.1. Materials and methods

The focus of this prospective, single-center documental field research was on blood product-free liver transplants. Data collection was carried out at the Department of Transplantation and Surgery, Semmelweis University, Hungary and referred to a period between July 2015 and December 2018. As a first step, the Massicotte's "2 units of blood transfusion" and "less than 900 ml bleeding" predictive nomograms were checked prior to the liver transplantation surgery in order to identify recipients of our study cohort for whom bloodless liver transplantations could be expected. As a second step, the patients' names were coded to ensure anonymity and data were collected prospectively from the patients' medical records. Hemostatic changes of fifty-nine blood product-free liver transplantations were analyzed. These patients did not receive even coagulation factor supplementation within 48 hours from surgery. Exclusion criteria included presence of acute liver failure, patient refusal and age < 18 years.

Liver transplantation procedures were performed by cross-clamping standard technique without veno-venous bypass, the graft was flushed with 200-300 mL of the recipient's own blood and all patients were given the same kind of anesthetic. All patients required intraoperatively endotracheal intubation, dual arterial line, triple lumen central line, peripheral line insertions, and Foley catheter, along with Salem sump (double-lumen gastric tube) placement. An experienced surgical team guaranteed that the total blood loss was minimized in every studied case in the absence of a cell saver instrument. Postoperatively, all patients were treated at the intensive care unit (ICU) during which stay standardized treatment and immunosuppressive protocols were followed. Demographic data of the patients, transplantation specific severity scores (DRI, MELD: Model for End-Stage Liver Disease), were recorded along with surgical, cold- and warm ischemia times (CIT, WIT) and supportive therapy. The need for supportive therapy,

extent of organ dysfunction, ICU LOS, hospital LOS, perioperative complications, morbidity and the survival rate were also recorded.

Hemodynamic monitoring was performed by transpulmonary thermodilution technique (PiCCO2 monitor: Getinge, Pulsion Medical Systems AG, Germany). Intraoperative fluid balance was aimed to be kept corresponting to (in accordance with) estimated hourly losses: urine output, insensible loss of the surgical site (2 mL/kg/h), the graft preservation solution flush with the patient's own blood, accidental surgical blood loss (surgical suction) in the absence of a cell saver instrument. The total intraoperative fluid balance was calculated on the basis of lost and administered fluids. In case of normovolemia, hypotension after graft reperfusion was treated with vasopressor. However, fluid replacement and vasoactive support was applied in combination to maintain a tolerable hypovolemia/vasoplegia, hence the treatment was adapted to the patient's momentary hemostatic and hemodynamic status. Postoperatively a zero fluid balance was aimed based on hourly losses and fluid replacement. In case of hypocalcaemia calcium replacement was performed through a continuous infusion pump or as a bolus injection according to the institutional protocol. The liver graft blood flow was monitored daily by a radiologist by Doppler ultrasound scan. Blood samples were obtained according to our institutional LT protocol and analyzed with conventional coagulation testing (CCT) and TEG. Standardized laboratory assays and hemostatic tests (factor I, II, V, VII, X, XIII, antithrombin III), hematocrit and platelet levels, total and direct bilirubin levels, liver enzimes (ALP, GOT, GPT, GGT, LDH) were carried out by Sysmex CS 2000i, Sysmex XN-1000 (Sysmex Europe GmbH, Hungary) and Dimension® RxL Max® Integrated Chemistry System (Siemens Healthcare GmbH, Hungary) instruments. Thrombelastography (TEG) was performed by Haemonetics® TEG 5000 Thrombelastograph Hemostasis Analyzer System (Haemonetics Corp., Switzerland). In the absence of clinically manifest coagulopathy or non-coagulopathic bleeding, the correction of intraoperative TEG parameters was not initiated. All measurements were performed at scheduled measuring times: before LT (T1- End stage liver disease (ESLD) hemostasis), end of LT (T2-hemostasis after surgery), 12 hrs after LT (T3-early graft function), 24 hrs after LT (T4-early graft function) and 48 hrs after

LT (T5- graft function). Whole blood coagulation was measured by thromboelastographic standard kaolin assay (TEG 5000, Haemonetics®) before LT (T1) and on arrival at the ICU (T2). TEG parameters (reaction time [R], maximal amplitude [MA], clot lysis at 60 minutes [Ly60]) were registered before LT (T1) and at the end of LT (T2).

3.2. Research phase II. Defining the perioperative hemostatic reserves

3.2.1. Materials and methods

As previously detailed in the Phase I of the research, coagulation factor specific hemostasis reserves were examined in 59 patients who received blood product-free liver transplantation. The volume-based coagulation factor specific blood losses were calculated according to the Gross method and trigonometric, according to baseline and „coagulopathic" trigger levels. The hemostatic reserves were also compared on the basis of the Child-Pugh classification. The conventional laboratory tests and the calculation of coagulation factor specific volume reserves were done/performed before LT (T1), after LT (T2), and after 12-24-48 hours (T3-T4-T5).

The method of the coagulation factor specific allowable blood loss

The allowable blood loss was calculated according to the Gross method at five predetermined times (T1-T5):

$$\text{Allowable blood loss} = \frac{\text{Blood volume} * 2 * (\text{Actual lab. level} - \text{Trigger level})}{(\text{"Actual lab.level"} + \text{"Trigger level"})}$$

The trigger levels of hemostatic interventions were: hematocrit<27%, platelets<30 G/L, FI<1g/L, FII-V-VII-X<30%, AT III<40% and FXIII< 60%, expressed in (mL) milliliters. The coagulation factor specific allowable blood losses were designated/named collectively as volume-based „total hemostasis reserve" and were represented on a radar diagram. The area under the curve of the radar diagram was obtained from the sum of the areas of the ten different triangles formed by the ten factors and expressed in L^2. The area of each triangle was calculated based on a trigonometric

area formula, where “a” and “b” are the values of the adjacent factors forming the given triangle.

3.3. Research phase III. Examination of the nursing workload and procedures

3.3.1. Materials and methods

The growing number of bloodless liver transplants in Hungary is based on the application of new techniques, which also entails some changes in nursing activities. Facing the new challenges, the aim of this descriptive, documental field research was to evaluate the kinetics of nursing activities and nurse/patient ratio in the first perioperative 48 hours of blood product-free liver transplantations.

Over the last few decades, several scoring systems were developed for use in critically ill patients not only to help therapeutic decision making but also to guide resource allocation and quality of care. We carried out some research in the scientific literature to find a score system that is appropriate for the analysis of this special group of patients.

The TISS score is a validated score system to define the nursing work time and nurse/bed ratio in the ICU. In 2000, TISS-28 was upgraded by the King's College Hospital (“King’s-TISS”) on 138 nursing activities specific to liver transplantation. However, it was not validated to determine the nursing worktime and nurse/patient ratio.
As previosusly detailed in Phase I of the research, 59 blood product-free liver transplanted patient's documents were analyzed prospectively.
Two electronic spreadsheets were used, composed of all the variables from TISS-28 score and all the 138 nursing activities/interventions according to “King’s-TISS” score. Each time when an intervention was prescribed for a patient it was indicated in the spreadsheet.
Nurse working time was calculated through the proportionality of the activities by a statistician. Regression techniques, Pearson’s correlation were used for the comparison of TISS-28 with “King’s-TISS” with a regression formula of ($\bar{y} = a + b * x$).
Focused on nurse/patient ratio, the proportionality of activities was compared between TISS-28 and “King’s-TISS” items. The correlation between 295 measurements points

was analyzed in 59 patients at the five pre-scheduled times: anesthesia (T1-anesthesia nursing), on arrival at the ICU (T2-intensive care nursing) and 12-24-48 h after LT (T3-4-5 intensive care nursing).

According to the primary goal, the "King's-TISS" score's 138 nursing activities were scored by organ systems (respiratory-, cardiovascular-, renal-, neurologic-, metabolic-, hemostasis-, immunology support) and nursing procedures (basic nursing care, monitoring, invasive interventions). The procedure specific and organ support specific nursing activity changes (Δ scores) were scrutinized on the timeline (over 48 hours) at five predetermined times (T1-T5).

Statistical Analysis

Results are expressed as mean ± standard deviation of the mean (SD) and confidence intervals (CI) of 95%. The normality of data was checked by applying the Shapiro-Wilk's test. When non-normal data could not be rejected, homogeneity of variances was assessed via the Levene's test. Means were compared by repeated measures analysis of variance (RANOVA) with Tukey's correction for multiple comparisons applied where appropriate. Pearson chi-square test ($\chi 2$) or Fisher's exact test was applied to sets of categorical data.

The analysis was two-sided, with a level of significance of $\alpha = 0.05$. All statistical analyses were done using the SPSS 25.0 (SPSS Inc., Chicago, IL) software package. For offline data analysis and graph creation a commercial software package was used (Microsoft Excel 2016).

Ethics License and Research ID:

This study followed the Declaration of Helsinki and was approved by the Local Ethics Committee of Semmelweis University (149/2016) and registered on Clinical Trials.gov on the 13th June 2018 (NCT03555383).

4. Results

4.1. Research phase I. The results of the perioperative kinetics of coagulation factors

In our study, the most common indications of liver transplantation were primary sclerosing cholangitis, hepatitis C viral infection, and autoimmune hepatitis. The patients were middle aged with slightly overweight body mass index (BMI) with a low MELD and average Child Pugh score, the median ICU LOS was 4 days IQR:2, the median hospital LOS was 15 days IQR:6. Based on Massicotte's predictive nomograms, the risk of the need for more than 2 units of blood transfusion was 2% and the risk of bleeding more than 900 mL during liver transplantation was 36%. The registered intraoperative bleeding was 1174 ± 490 mL, (CI: 1046–1303) calculated from the blood loss from the pool of the explanted liver, the graft flushing with own blood (graft size) and the accidental bleedings (surgical suction). The intraoperative fluid balance was 611 ± 896 mL (CI: 377-844) according to measurable input (crystalloid and colloid, albumin 5%, 20%) minus measurable output (blood loss and urine output) and insensible losses. According to the study protocol, none of the patients needed red blood cells (RBCs), fresh frozen plasma (FFP), platelet or coagulation factor (fibrinogen, PCC) replacement at all to compensate for intraoperative bleeding. The preoperative ESLD related clotting factor (CF) levels are listed as fibrinogen (FI) 2.9 g/L, FII 77%, FV 89%, FVII 81%, FX 88%, FXIII 121%, ATIII 90%. A significant intraoperative decrease in the CF levels was observed at the end of LT: the fibrinogen level decreased by 1,2 g/L, the other studied factor levels decreased by 26–-40% (T1-T2, P <0,001). An increase in the fibrinogen levels by 0.9 ± 0.6 g/L was observed at the end of the first postoperative day parallel/along with the increases of factor II, V, VII, X levels by 12%, 20%, -31%, respectively. These increases at the end of the second postoperative day were associated with good graft function. However, FX reached only half of the T1 level at the second postoperative day with a value of 12 % (T3-T5, P < .001). The FXIII remained continuously low in the postoperative 2 days. (Figure 1)

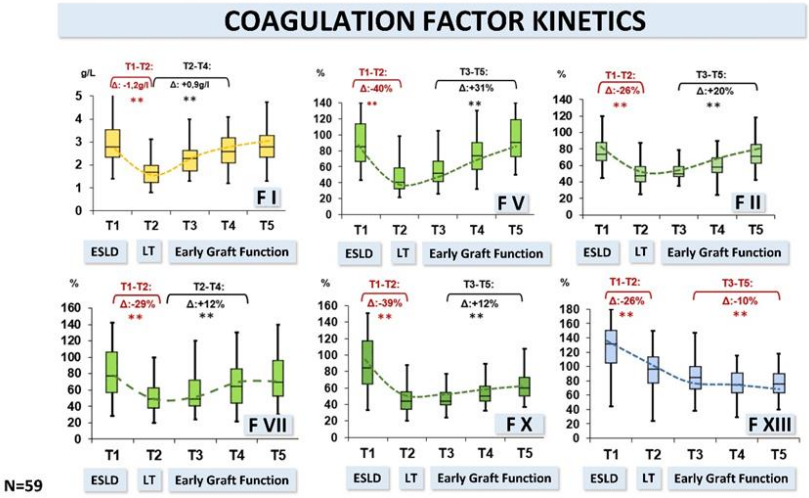

Figure 1. Kinetics of coagulation factor levels during blood product-free liver transplantations related to the first 2 perioperative days (N=59).

Measurements of FI (fibrinogen), FII (prothrombin) and FV-VII-X-XIII were performed before liver transplantation (T1), end of LT (T2) and 12-24-48 hrs after transplant (T3-T4-T5). Data are shown as means, median and interquartile ranges. Intraoperative: FI-II-V-VII-X-XIII decrease T1-T2, P < .01; Postoperative: FI increase T2-T4, P < .01, FII-V-VII-X increase T3-T5, P < .01, decrease FXIII T3-T5, P < .05. (The mean difference is significant if **P < .01, FI: factor I; FII: factor II; FV: factor V; FVII: factor VII; FX: factor X; FXIII: factor XIII.)

Platelet count had raised by 36±43 G/L (CI: 21-51) in 36 patients by the end of surgery (T1-T2, p = .04). Regarding all patients, the platelet count improved by 3,3 ± 53 G/L (CI: -10–-17) (T1-T2, P = 0,62).

Intraoperative thromboelastographic standard kaolin assay (TEG 5000, Haemonetics) showed minimal increase in clotting rate, kinetics and fibrinolysis, slight decrease in clot amplitude but all parameters remained in the non-coagulopathic range. Hemodynamic data are summarized in Fig 4. Intraoperative central venous pressure (CVP) level was

found to be 6 ± 2.9 mmHg, (CI:5.2–6.7). The cardiac index ranged between 3.4±1.3 l/min/m2 (CI:2.9–3.8). The values of intrathoracic blood volume index (ITBI) of 785 ± 139 mL/m^2 (CI: 746–824) indicated relative normovolemia of the cohort. Cardiac index of 3.4 ± 1.3 L/min/m2, (CI: 2.9–3.8) and MAP of 93 ± 12 mmHg, (CI: 90–97) were considered adequate during hepatectomy and in the anhepatic phase. The CVP and the Cardiac Index started to increase after graft reperfusion, but significant differences were observed only at the end of surgery (T1-T2: ΔCVP 2.4 ± 4.6 mmHg, ΔMAP: 4.3 ± 13 mmHg, change is the Cardiac Index:1.2 ± 1.3 L/min/m2). Patients required a peak dose of 0.15 ± 0.13 μg/kg/min norepinephrine to maintain adequate MAP. In the postoperative period relative normovolemia, normal filling pressures and good perfusion pressure were detected and cardiac index also increased significantly. The vasopressor support was stopped within 24 hours after transplantation in all studied patients except seven patients requiring vasopressor therapy for more than 48 hrs. The graft quality in our study was characterized by lower (1,5 ± 0,3; CI: 1,4–1,5) donor risk index. Reviewing the surgical complications, we can conclude that no reoperation was done in the first 48 hours. The 93% of blood-free liver transplant recipients are still alive 5 years after the transplant/intervention.

4.2. Research phase II. Results of the perioperative hemostatic reserves

The volume-based hemostatic reserves of platelet, FV-VII-X and fibrinogen, calculated by Gross method, showed a reserve of more than 75% relative to total circulating blood volume. The reserves of FII-XIII and hematocrit and AT III showed a reserve of more than 50% relative to total circulating blood volume. Coagulation-specific reserves were significantly decreased at the end of liver transplantation. Prothrombinase (V-X) and hematocrit reserves were reduced by half of the initial level. The decrease in fibrinogen, FVII and AT III reserves showed 30% relative to total circulating blood volume. The decrease of FII-XIII reserves showed 25% relative to total circulating blood volume. On the other hand, no alteration had appeared to the platelet-based reserves by the end of OLTx. The kinetics of volume-based hemostatic reserves showed the same tendency as the kinetics of the factor levels after liver transplantation. The reserve of fibrinogen

normalised over 24 hours. ($p < .001$). The reserves of FII-V-VII-X increased in a slower rate and these reserves had just approached the baseline values over 48 hours (T3-T5, $p < .001$). The hemostasis total reserves, which were calculated from the area under the curve, had decreased from 58 ± 40 L^2 by 61% by the end of LT (T1-T2; $p < .001$). The total reserves increased after the surgery, and had reached 88% of the initial/baseline levels by the second postoperative day. (Figure 2)

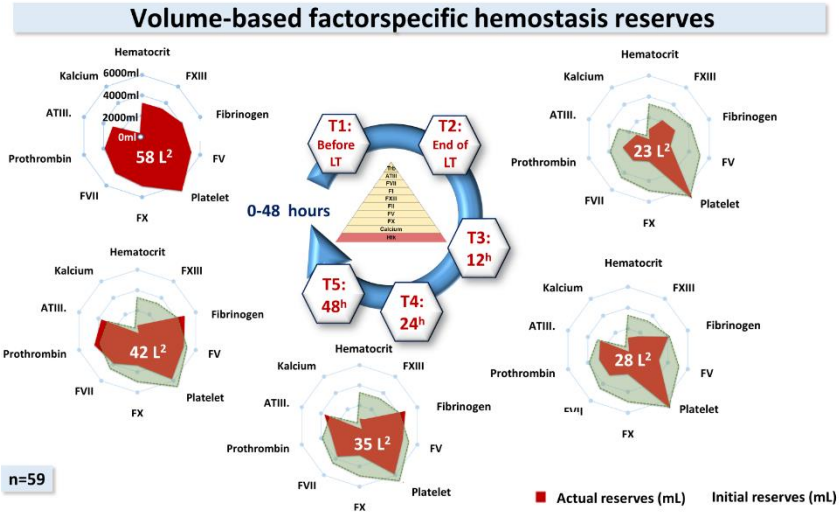

Figure 2: The volume based factorspecific hemostatic reserves

The measurements were performed in 59 patients at five pre-scheduled times: under LT (T1-anesthesia nursing), on arrival at the ICU (T2-intensive care nursing) and 12-24-48 h after LT (T3-4-5 intensive care nursing). Mean values of factor-specific allowable blood losses are visualized in the radar diagram. The smallest reserve is indicated in the center of the radius (0 ml), then moving outwards within the radius, each parameter is displayed, the current (green) and the preoperative initial volume (red) expressed in milliliters. The area under the curve illustrates the volume-based total hemostasis reserves (L^2) Abbreviations: AT III: antithrombin III, Htk: hematocrit, F I: (fibrinogen) factor I, F II: (prothrombin) Factor II, F V: factor V, F VII: factor VII, F X: factor X, F XIII. factor XIII, OLTx: orthotopic liver transplantation

When the severity of liver failure was also taken into consideration, the initial total reserves in the decompensated Child-Pugh group B and group C were lower (by 36% and 41%, respecively) compared to the values found in the group Child-Pugh A . However, there was no significant difference between the coagulation-specific reserves by the second day.

4.3. . Research phase III. Results of the nursing workload and procedures

The total of TISS-28 points were decreased by 50% in the first day, the "King's-TISS" score points were decreased by ≥ 20% daily (T1-T2, T2-T5 p = .001).

Strong correlation was observed between "Kings-TISS" and TISS-28 scores during the research period (T1-T5), the TISS-28 explains 44% of the variation in Kings-TISS (r equals .666, r2 equals .44, p≤.001). Only (eighteen) 18 of 28 (64%) analyzed TISS-28 items vs. 67 of 138 (48%) analyzed "King's TISS" items were matched during the study period. Considering the unstandardized regression coefficient and the ratio of matched items, the difference between the two methods is almost 30%. Considering that each TISS-28 point corresponds to 10.6 work time in minutes, one King's-TISS point equals 7,4 work time in minutes. In other words, a typical ICU nurse is capable of delivering work which equals almost 97 "King's-TISS" points during a 12-hour shift. (Table 1)

Table 1. The sum of "Kings-TISS" score points, matched items, nursing work time and the nurse/patient ratio in blood product-free liver transplanted patients.

Sum of "Kings-TISS" score								
		During LT (T1)	**ICU (T2)**	**12h (T3)**	**24h (T4)**	**48h (T5)**	**p value**	
							T1-T2	**T2-T5**
"King's-TISS" points	Median (IQR)	105 IQR: 0	100 IQR: 12	85 IQR: 9	79 IQR: 9	73 IQR: 6		
	Mean (SD)	104±3.5 (CI:104 -105)	100±7 (CI:98 -102)	86±8 (CI:84 -89)	79±7 (CI:77 -80)	73±7 (CI:71 -74)	p < .001	p < .001
Working hours per 12 hours shift		12.9± 0.4 (CI:12.1 -12.3)	12.3± 0.9 (CI:11 -12)	10.4± 0.9 (CI:10 -10.5)	9.7± 0.6 (CI:9- 9.5)	9± 0.8 (CI:8.4- 8.8)	p < .001	p > .001
Nurse patient ratio		2:1	1.5:1	1:1	1:1	1:1- 1:1.5		

The nursing intervention grouped by organ support showed heterogeneous changes, some activities decreased significantly or vanished, others (like monitoring, basic nursing care and supportive nursing activites concerning metabolism, hemostasis, and immunology) remained unchanged during ICU follow-up. (Figure 3)

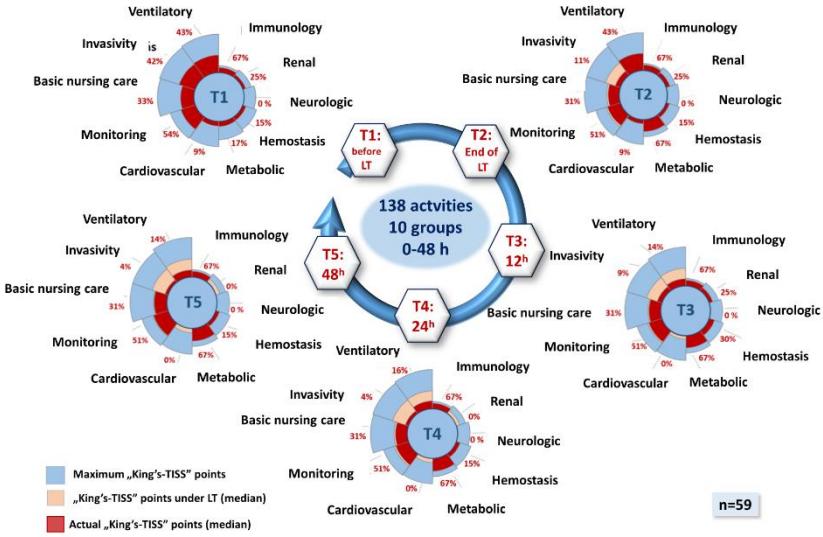

Figure 3: Kinetics of the King's TISS Score points grouped by organ support and nursing activities (procedures) during the procedures of blood product-less liver transplantations and in the first 48 hours afterwards.

The "Nightingale rose diagram" displays the kinetics of the median King's-TISS" score (according to) grouped by nursing procedures and organ support items, and also shows the percentage of the reached scores in relation to the maximum points. Abbreviations: ICU: intensive care unit, OLTx: Orthotopic liver transplant

5. Conclusions

In this clinical research/study I firstly analyzed the perioperative kinetics of coagulation factors, then the changes in the factorspecific volume-based hemostatic reserves, and finally I invesigated the performed nursing activities in an organ-specific approach in 59 blood product-free liver transplanted patients.

The following conclusions can be drawn taking into account our hypotheses listed in the objective:

1. Firstly having studied perioperative changes in the levels of coagulation factors and the extent of the inevitable decrease in hemostasis reserves, we conclude that the procedure of an "ideal" liver transplant seems to reduce fibrinogen levels by 1.2 g/L in average and other coagulation factors (FII, V, VII, X) by 30–40% until the end of the surgery.
2. If preoperative baseline fibrinogen levels of the recipients are above 2.2 g/L, no severe portal hypertension is present, no surgical complications can be expected, and positive fluid balance can be avoided, a successful transplantation can be expected without the need for administration of any blood products or coagulation factor preparations.
3. As part of the acute phase reaction, the synthetic function of the graft partially restores the levels of coagulation factors to the preoperative level: firstly fibrinogen, by the first postoperative day, than the levels of coagulation factors (FII, V, VII, X) by the second day. Thus, the kinetics of coagulation factor levels draw a "tick mark" shaped curve during bloodproduct-free liver transplantation.
4. In addition to the evaluation of the kinetics of coagulation factor levels, we carried out viscoelastic tests as well. Viscoelastic properties of the blood demonstrated a well-balanced and coagulopathy-free clotting with an appropriate amplitude suggesting the compensatory role of platelets.
5. A preplanned, goal-directed, individualized intraoperative hemostasis management could be implemented on the basis of the evaluation of perioperative hemostatic

reserves, and the probability of blood product-free liver transplants could be estimated.

6. The volume-based approach to hemostasis can dynamically indicate the current hemostatic reserves and helps to adjust the treatment to the individual needs of the patient.
7. Information about hemostatic volume reserves is helpful for the staff to avoid iatrogenic hemodilution, by expressing in milliliters the reserve of the weakest link in the system.
8. The unconventional, volume-based approach to hemostasis might enable bloodlessness in surgical procedures with a higher risk of bleeding.
9. The early postoperative period implies significant (relevant) haemostatic disturbances in liver-transplanted recipients until a balanced haemostatic state is achieved by the graft-related production of coagulation factors. The balance in hemostasis is the most “vulnerable” when the levels of blood coagulation factor reserves are lowest. Accordingly, this is when the majority of nursing activities are required, especially close monitoring of hemostasis.
10. The King’s-TISS score a reliable indicator of disease severity and nursing workload but does not analyze the novel techniques of viscoelastic assays and administration of coagulation factor concentrates. Therefore the score has to be improved and updated to be eligible to the new challenges.
11. Based on this first validation of the scoring system, the “King’s-TISS” points equal 7,4 minutes of each nurse's shift. Thus, the nurse/patient ratio equals 2:1 intraoperatively and 1:1 postoperatively even in uncomplicated cases of blood product-free LTs.

6. Author's Publication List

Publication in relation to the dissertation; original articles, Értekezés témájához kapcsolódó közlemények

Original articles

1. **Rengeiné Kiss T**, Tihanyi E, Dinya E, Smudla A, Kóbori L, Kanizsai P, Fazakas J Mapping the nursing interventions by Therapeutic Intervention Scoring System in bloodless liver transplantations Intensive Crit Care Nursing, XX, p XX (2020) Article in press
   DOI: 10.1016/j.iccn.2020.102917 **IF: 1,886**
2. **Rengeiné Kiss T**, Máthé Z, Piros L, Dinya E, Smudla A, Mándli T, Kóbori L, Doros A, Kanizsai P, Fazakas J How much is the "inevitable" loss of different coagulation factors during blood product free liver transplantations? Transplantation Proceedings, XX, p. 1-8 (2020), Article in press DOI: 10.1016/j.transproceed.2020.05.006 **IF: 0,784**
3. **Rengeiné Kiss T**, Smudla A; Dinya E; Kóbori L; Piros L; Szabó J; Máthé Z; Illés S; Mándli T; Szabó T; Szabó M; Tóth Sz; Tőzsér G; Túri Cs; Füle B; Kanizsai P; Fazakas J Térfogatalapú haemostasistartalékok vérmentes májtranszplantációk során [Volume-based haemostasis reserves in blood product free liver transplantations]. Orv Hetil, 2020. 161 (7): p. 252-262.
   DOI: 10.1556/650.2020.31652 **IF: 0,497**

Publication concerning the scientific work

1. **Rengeiné Kiss T**, Máthé Z, Piros L, Dinya E, Tihanyi E, Smudla A, Fazakas J The hemostasis changes in bloodless liver transplantation CRITICAL CARE 21:(Supl 1) pp. 30-31. (2017) 37th International Symposium on Intensive Care and Emergency Medicine. Bruxelles, Belgium: 2017.03.21 -2017.03.24. DOI: 10.1186/s13054-017-1628-y
2. **Rengeiné Kiss T**, Máthé Z , Piros L, Dinya E, Mándli T, Tóth Sz , Smudla A, Illés S, Szabó T, Szabó M, Fazakas J Kinetics of Hemostasis Reserve Capacity in

Bloodless Liver Transplantation TRANSPLANTATION, 101: (5 Suppl 2): p. 65. (2017) In: The 2017 International Congress of ILTS, ELITA & Licage Prague, Czech Republic: 2017.05.24 -2017.05.27.
DOI: 10.1097/01.tp.0000520180.40625.72

Other publications

1. **Rengeiné Kiss T**, Fazakas J Az első magyarországi csecsemő májtranszplantáció során szerzett intenzív terápiás tapasztalatok: esetismertetés In: Aneszteziológia és Intenzív Terápia. 2013. 43. évf. 1. sz., p. 34-38. ISSN 0133-5405.
2. **Rengeiné Kiss T**, Fazakas J, Ujhelyi E Szakmai összefogás egy akut májelégtelen gyermekért: esetismertetés Gyermekgyógyászat. 2012. 63. évf. 6. sz., p. 302-306. ISSN 0017-5900.

Chapters of books

1. Fazakas, J; Horváthné, Komjátszegi G; **Rengeiné Kiss T**: Szervtranszplantáció In: Dr. Ujhelyi, Enikő (szerk.) A gyermekápolás elméleti és gyakorlati alapjai Budapest, Magyarország: Medicina Könyvkiadó Zrt., (2019) pp. 1075-1091., 17 p. Közlemény: 30432862 Jóváhagyott Forrás Könyvrészlet (Chapter of book)
2. Hirlemann, I; Horváthné, Komjátszegi G; **Rengeiné, Kiss T**: Ágy melletti vizsgálóeljárások ápolói teendői. Mintavétel laboratóriumi vizsgálatokhoz In: Dr. Ujhelyi, Enikő (szerk.) A gyermekápolás elméleti és gyakorlati alapjai Budapest, Magyarország: Medicina Könyvkiadó Zrt., (2019) pp. 575-596., 22 p. Közlemény:30432824 Jóváhagyott Forrás Könyvrészlet (Chapter of book)
3. Nagy, R; **Rengeiné, Kiss T**: Extracorporalis kezelések In: Dr. Ujhelyi, Enikő (szerk.) A gyermekápolás elméleti és gyakorlati alapjai Budapest, Magyarország: Medicina Könyvkiadó Zrt., (2019) pp. 1072-1074., 3 p. Közlemény:30432834 Jóváhagyott Forrás Könyvrészlet (Chapter of book)
4. Hirlemann I, Horváthné Komjátszegi G, **Rengeiné Kiss T**: Ágy melletti vizsgálóeljárások In: Biczó Annamária, Kovács-Császár Melinda (szerk.) Gyermekintenzív szakápolástan. 432 p. Budapest: Egészségügyi Nyilvántartási és Képzési Központ (ENKK), 2016. pp. 147-152. (ISBN:978 963 9661 06 6)

5. Kovács-Császár M, **Rengeiné Kiss T**: Extracorporalis technikák In: Biczó A, Kovács-Császár M (szerk.) Gyermekintenzív szakápolástan. 432 p. Budapest: Egészségügyi Nyilvántartási és Képzési Központ (ENKK), 2016. pp. 128-135. (ISBN:978 963 9661 06 6) (Chapter of book)
6. Rácz A, **Rengeiné Kiss T**: Invazív és noninvazív monitorizálási lehetőségek In: Biczó A, Kovács-Császár Me (szerk.) Gyermekintenzív szakápolástan. 432 p. Budapest: Egészségügyi Nyilvántartási és Képzési Központ (ENKK), 2016. pp. 53-67. (ISBN:978 963 9661 06 6) (Chapter of book)
7. **Rengeiné, Kiss T**: Szervtranszplantáltak ápolása pp. 300-316., 16 p. In: Biczó, Annamária; Kovács-Császár, Melinda (szerk.) Gyermekintenzív szakápolástan Budapest, Magyarország: Egészségügyi Nyilvántartási és Képzési Központ (ENKK), (2016) p. 432 Közlemény:3232789 Jóváhagyott Forrás Könyvrészlet (Chapter of book)
8. Fazakas, J ; Smudla, A ; **Rengeiné, Kiss T** Gyermekkori szervtranszplantációk intenzív terápiája In: Ujhelyi, Enikő (szerk.) A gyermekintenzív ellátás elmélete és gyakorlata Budapest, Magyarország: Medicina Könyvkiadó Zrt., (2014) pp. 167-171. Közlemény:2593639 Admin láttamozott Forrás Könyvrészlet (Chapter of book)
9. Fazakas J, Szabó T, **Rengeiné Kiss T**: Az akut májelégtelenség, In: Bogár L, Molnár Zs (szerk.) Az intenzív terápia gyakorlata. 579 p. Budapest: Medicina Könyvkiadó Zrt., 2013. pp. 469-479. (Chapter of book) (ISBN:978 963 226 440 0)