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Point-of-care haemostasis monitoring during liver transplantation reduces transfusion requirements and improves patient outcome

Antonio Leon-Justel [a,*], Jose A. Noval-Padillo [b], Ana I. Alvarez-Rios [b], Patricia Mellado [c], Miguel A. Gomez-Bravo [d], Jose M. Álamo [d], Manuel Porras [e], Lydia Barrero [d], Rafael Hinojosa [e], Magdalena Carmona [f], Angel Vilches-Arenas [g], Juan M. Guerrero [b]

[a] Laboratory Medicine Department, Huelva University Hospital (Institute of Biomedicine of Seville, Seville University), Spain
[b] Laboratory Medicine Department, Virgen del Rocío University Hospital, Seville (Institute of Biomedicine of Seville, Seville University), Spain
[c] Department of Anaesthesiology, Virgen del Rocío University Hospital, Seville, Spain
[d] Department of Hepatobiliary Surgery, Virgen del Rocío University Hospital, Seville, Spain
[e] Department of Intensive Care Medicine, Virgen del Rocío University Hospital, Seville, Spain
[f] Department of Haematology and Haemotherapy, Virgen del Rocío University Hospital, Seville, Spain
[g] Department of Preventive Medicine and Public Health, University of Seville, Spain

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ABSTRACT

Background: Optimal haemostasis management can improve patient outcomes and reduce blood loss and transfusion volume in orthotopic-liver-transplant (OLT).
Methods: We performed a prospective study including 200 consecutive OLTs. The first 100 patients were treated according to the clinic's standards and the next 100 patients were treated using the new point-of-care (POC)-based haemostasis management strategy. Transfusion parameters and other outcomes were compared between groups.
Results: Transfusion requirements were reduced in the POC group. The median and IQR of red-blood-cells (RBC) transfusion units were reduced from 5 [2–8] to 3 [0–5] ($p < 0.001$), plasma from 2 [0–4] to 0 ($p < 0.001$), and platelets from 1 [0–4] to 0 [0–1] ($p < 0.001$), into the POC group only four patients received tranexamic acid and fibrinogen transfusion rate was 1.13 ± 1.44 g ($p = 0.001$). We also improved the incidence of transfusion avoidance, 5% vs. 24% ($p < 0.001$) and reduced the incidence of massive transfusion (defined as the transfusion of more than 10 RBC units), 13% vs. 2% ($p = 0.005$). We also observed a relationship between RBC transfusion requirements and preoperative haemoglobin, and between platelet transfusion and preoperative fibrinogen levels. The incidence of postoperative complications, such as, reoperation for bleeding, acute-kidney-failure or haemodynamic instability was significantly lower (13.0% vs. 5%, $p = 0.048$, 17% vs. 2%, $p < 0.001$, and 29% vs. 16%, $p = 0.028$). Overall, blood product transfusion was associated with increased risk of postoperative complications.
Conclusions: A haemostatic therapy algorithm based on POC monitoring reduced transfusion and improved outcome in OLT.

1. Introduction

Orthotopic-liver-transplantation (OLT) has become the first-line approach for the treatment of patients with end-stage liver disease [1,2]. As a result of improvement in anesthesiological and surgical skill, organ support device adoption, advanced understanding of transplant immunology, and better critical care management of complications, liver transplanted patients survive longer. However, OLT has been associated with severe bleeding and subsequent massive transfusion of allogeneic blood products, such as plasma, platelets and red blood cells (RBC) [3]. Substantial evidence suggests that the use of blood products during OLT is associated with a number of post-operative adverse events and may negatively affect the evolution of the procedure, resulting in a limited success on an individual basis [4,5]. High volume of fresh frozen plasma (FFP) transfusion is considered as a predictor of postoperative bleeding risk [6] and platelet transfusion has also been identified as an independent risk factor for adverse postoperative outcomes [7].

Severe bleeding in OLT is related to both existing co-morbidities and the procedure itself [8]. Due to the complex nature of the haemostatic response to surgery, an interaction of plasma proteins, platelets, and the vessel wall [9], routine laboratory plasma coagulation tests running in the main laboratory, such as international normalised ratio (INR) and

* Corresponding author at: Laboratory Medicine Department, Huelva University Hospital, Ronda Exterior Norte, s/n, 21005 Huelva. Spain. Tel.: +34 677904265.
E-mail address: antonio.leonj.sspa@juntadeandalucia.es (A. Leon-Justel).

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activated partial thromboplastin time (aPTT), are not sufficient to diagnose specific coagulation defects and to guide haemostatic therapy. Instead, whole blood monitoring strategies sensitive to all major pathomechanisms are more informative. In OLT surgery, where events often progress at a fast and dramatic pace, minimising the delay in collecting test results from a central laboratory is critical to efficient haemostasis management. However, determining the optimal approach to diagnosis and treatment of defective haemostasis remains one of the greatest challenges in OLT [10,11].

Point-of-care (POC) testing may overcome some of the limitations of traditional approaches to haemostasis management [12,13]. In contrast to routine coagulation tests, results from POC devices can be obtained within a few minutes, allowing goal-directed therapy to be rapidly initiated. In addition, POC testing allows the differential diagnosis of specific coagulopathies. The use of POC-guided haemostatic therapy is critical in optimising massive transfusion management and reducing overall blood loss [14,15], and recent guidelines recommend the inclusion of POC coagulation monitoring in the perioperative management of bleeding patients [16,17]. Despite the large number of published studies in this area, precisely how haemostatic assessment should be carried out in the setting of OLT is not clearly defined in the literature. Although multiple trials have evaluated different approaches to haemostatic management in other settings [18,19,20], the evidence in other surgical settings with substantial blood loss, such as OLT, is lacking.

In this study, we evaluated the impact of a new approach for haemostatic and transfusion management based in POC monitoring in OLT. Our first aim was to evaluate the impact on transfusion requirements; numbers of units of blood product given per patient intraoperatively, the proportion of patients who completely avoided blood product transfusion (total avoidance), and the proportion of patients who received massive transfusion (defined as the transfusion of more than 10 RBC units). The second aim was to evaluate the impact in adverse patient outcomes, defined as the rate of occurrence of immediate postoperative complications.

2. Materials and methods

2.1. Study population

We evaluated 200 consecutive OLTs performed at the Virgen del Rocio University Hospital in Seville, Spain, between October 2009 and July 2012. This study was performed following approval of the VRUH ethics committee (PI/132) and in accordance with the Declaration of Helsinki and Good Clinical Practice. Informed consent was obtained for all patients. Patient characteristic, details of the surgery, transfusion requirements, laboratory test results and immediate postoperative complications were prospectively recorded in a computerised database. Patients on the waiting list for OLT were prioritised using the Model for End-stage Liver Disease Score (MELD). Four hepatobiliary surgeons (with two surgeons present during each transplant procedure) and seven anaesthesiologists were available as part of the OLT team. Grafts were taken from cadaveric donors and transplantation procedures were all performed using the piggyback technique. Reduced-size graft and age < 18 yr were considered as exclusion criteria.

2.2. Study design

We performed a prospective study including 200 OLT to evaluate the impact in transfusion requirement and patient outcomes of the new approach for haemostasis and transfusion management based in POC monitoring in comparison with the current standard procedure based in routine testing performed in the main laboratory. 200 consecutive OLTs were studied into two different groups according with the haemostasis management strategy: the first group included 100 consecutive OLTs for which haemostasis was assessed using the current standard procedure and the second group included the next 100 consecutive OLTs for which haemostasis was assessed using the new POC-approach. Blood samples, for both groups, were taken at preestablished time points during OLT: after induction of general anaesthesia, at the end of the hepatectomy, 20 min after vascular clamping, and 20 min after graft revascularisation. The blood samples were collected from a nonheparinised arterial catheter after discarding the first 10 mL.

In the "*Standard-care group*" (*SCG*) haemostasis and transfusion management was assessed supported by routine laboratory testing performed at the main laboratory. The transfusion management of unusual complications was decided according to a preestablished guideline. RBCs were transfused to maintain the haemoglobin (Hb) level higher than 7 g/dL. Transfusion of non-RBC blood products was based on clinical grounds and guided by the results of the standard coagulation tests according with specific protocol. The thresholds for selecting plasma, and PLTs were INR of greater than 1.6, plasma fibrinogen level of less than 1.0 g/L, and PLT count of less than 70×10^9/L, respectively. Ionised calcium (iCa) level maintained >1 mmol/L and pH >7.2 with 8.4% sodium bicarbonate. Cobas® 6000 modular analyser (Roche Diagnostic, Mannheim, Germany) was used to measure glucose, sodium, potassium and creatinine (Jaffe method) serum levels; pH and iCa were analysed in a ABL800-FLEX® blood gas analyser (Radiometer Medical A/S, Bronshoj, Denmark); haemogram was recorded using a XE-2100 counter (Sysmex, Mundelein, IL, USA); plasma coagulation tests: INR, aPTT and fibrinogen, were performed on ACL-TOP-500® (Instrumentation Laboratory, Bedford, MA, USA).

In the "*POC group*" (*POCG*) haemostasis and transfusion management was decided according to a specific algorithm based in Mobile-laboratory-unit (MLU) results (Fig. 1) placed in the operation room. The concept of the MLU has been developed at our centre [21], to provide immediate rapidly diagnose coagulation disturbances and guide goal-directed haemostatic therapy at the patients' bedside. The MLU is a new fully flexible POC device capable of performing a broad menu of tests on a single portable platform, including routine biochemistry, haematology and coagulation tests, allowing for the monitoring of all major pathomechanisms related with the hemorrhages. The unit we formed to support OLTs includes: a Cobas® b 221 (Roche Diagnostic, Mannheim, Germany) to perform blood gas analyses and record pH, glucose, sodium, potassium, iCa and lactate levels; a pocH-100i cell counter (Sysmex, Mundelein, IL, USA), and a ROTEM® device (ROTEM, TEM International GmbH, Munich, Germany) for real time haemostasis monitoring using the extrinsically activated test (EXTEM) and the fibrin-based clot test (FIBTEM). Coagulation time (CT), clot formation time (CFT), clot amplitude after 10 min (A10), and maximum clot firmness (MCF) were recorded for the EXTEM test while A10 and MCF were recorded with the FIBTEM test. Blood samples were tested immediately after collection by a laboratory technician under supervision of a clinical pathology.

2.3. Statistical analyses

All statistical analyses were conduced using software with the Statistical Packed for the Social Sciences (SPSS version 20.0, Chicago IL, USA). A descriptive analysis was carried out using qualitative variables, represented in the tables as absolute frequencies and percentages. Quantitative variables were expressed using mean and standard deviation (SD) or median and interquartile range [IQR] [p25–p75] as appropriate. Differences between groups were tested using the Mann–Whitney U-test, the Pearson Chi-Square test or Fisher's exact test, as appropriate.

Multivariate analyses were performed, using logistic regression and linear regression model, to describe the relationship between transfusion events, considered as dichotomous dependent variable (yes or not) and continuous variable (units of RBC, plasma and platelets transfused), and a set of independent variables (hypothetical predictive factors). The model included the haemostasis management approach as dichotomous variable (standard-care vs. POC). We selected the best set of predictive variables for transfusion event among those reaching