Transfusion and Apheresis Science 43 (2010) 401–405

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Goal-directed hemostatic resuscitation for massively bleeding patients: The Copenhagen concept

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ARTICLE INFO

Keywords:
Massive transfusion
Trauma
Coagulopathy
Thrombelastography
Fresh frozen plasma
Platelets
Red blood cells

ABSTRACT

Background: Continued hemorrhage remains a major cause of mortality in massively transfused patients, many of whom develop coagulopathy. A review of transfusion practice for these patients at our hospital revealed that a significant proportion received suboptimal transfusion therapy. Survivors had higher platelets count than non-survivors.
Methods: For massively transfused patients with hemodynamic instability, we introduced the concept of transfusion packages comprising five units of red blood cells, five units of fresh frozen plasma and two units of platelet concentrates. Thrombelastogram analysis was validated for routine laboratory use and implemented in the blood bank for monitoring coagulopathy and guiding transfusion therapy. Anaesthetists at our hospital were trained in functional haemostasis management based on analysis of thrombelastograms.
Results: Intraoperative administration of transfusion packages for patients operated on for a ruptured abdominal aortic aneurysm was associated with a reduction in mortality from 56% to 34% ($p = 0.02$). When comparing massively transfused patients treated with hemostatic control resuscitation, i.e., transfusion package therapy during hemodynamic instability and thromboelastogram – monitored and guided transfusion therapy, with controls treated in accordance with existing transfusion guidelines, mortality was reduced from 31% to 20% ($p = 0.002$).
Conclusion: The initiative from the blood bank, i.e., transfusion packages for patients with uncontrollable bleeding and based on the thromboelastogram when hemodynamic control is established, has improved the transfusion practice and survival in massively transfused patients at our hospital.

1. Background

Ongoing hemorrhage is a major predictor of mortality in massively transfused patients, and coagulopathy in turn is a major contributor to the ongoing hemorrhage [1]. It appears, however, that the resuscitation strategy influences coagulopathy and survival. The American Society of Anesthesiology (ASA) advocates early administration of crystalloids and colloids, while the administration of fresh frozen plasma (FFP) and platelet concentrates (PC) is advised only when one total blood volume has been replaced. [2] Patients who survive massive transfusion, defined as more than 10 units of red blood cells (RBCs) within 24 h, have a higher platelet count [3], shorter prothrombin time (PT) and shorter activated partial thromboplastin time (aPTT) [4] compared to non-survivors. Similarly, records from patients receiving more than 10 units of RBCs within 24 h and 30 units of blood components within 7 days reveal that the platelet count upon arrival at the intensive care unit (ICU) was 101×10^9/L in survivors compared with 44×10^9/L in non-survivors [5]. Of these patients, 14 developed perioperative microvascular bleeding (MVB), and only two survived. Some of the patients who developed MVB received

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doi:10.1016/j.transci.2010.09.002

less plasma and platelets than recommended in the ASA guidelines, but MVB also manifested in patients for whom the guidelines were followed.

It appears, therefore, that for massively bleeding patients, a platelet count of approximately 100×10^9/L rather than 50×10^9/L, as current guidelines recommend, is associated with improved survival following surgery. Furthermore, a significant proportion of massively bleeding surgical patients develops perioperative MVB even when transfused in accordance with current recommendations, thus affecting mortality. A likely explanation for the shortcomings of the current transfusion guidelines is that they do not consider individual differences in coagulation factor activity, platelet concentration, bleeding dynamics, extent of tissue damage and type of trauma when the transfusion strategy is planned [6]. Accordingly, it seems inadequate to base recommendations for the transfusion of massively bleeding patients on observations of patients going through elective surgical procedures. A further problem is that conventional coagulation analyses are used to identify coagulopathy even though they describe only isolated aspects of the hemostatic process [7].

2. Interventions

2.1. Thrombelastography (TEG)

The cell-based model of hemostasis emphasises the pivotal role of platelets for thrombin generation and also highlights the importance of the dynamics of thrombin generation in influencing the quality and stability of the thrombus formed [8]. Consequently, coagulation assays performed using plasma only are of limited value, and this explains the finding that activated partial thromboplastin time (APTT) and prothrombin time (PT) do not reflect clinically relevant coagulopathies or bleeding conditions [7,9]. Instead, it is preferable to use a hemostatic assay such as a thromboelastogram, which records viscoelastic changes during coagulation via analysis of *whole blood* placed in a rotating cup (Fig. 1) [10]. In this assay, a pin is suspended in the blood from a torsion wire, and its resistance to motion is recorded. Four parameters are routinely reported: reaction time (R) denotes the latency from the time when the blood is placed in the cup until the clot begins to form, the angle (Angle) represents the progressive increase in clot strength, the maximum amplitude (MA) reflects the maximal clot strength and lysis (Ly30) reflects clot lysis (Fig. 1).

Our group demonstrated that thrombus generation measured by TEG correlates with thrombin generation kinetics [11]. Coagulation factor deficiency and/or thrombocytopenia/thrombocytopathy may result in impaired thrombin formation and, in turn, impaired clot formation. Reduced clot stability, as evaluated by TEG, correlates with clinical bleeding conditions as elegantly demonstrated by Plotkin et al. [12] who reported that in patients with penetrating trauma, TEG was a more accurate indicator of blood product requirements than the PT or APTT. They recommended that TEG, supplemented by the platelet count and hematocrit, should be used to guide blood transfusion requirements. We concur with this recommendation. Furthermore, TEG is the gold standard for identifying hyperfibrinolysis, a significant cause of bleeding in major trauma, ischaemia/reperfusion injury, and obstetric calamities [13,14]. TEG analysis is now validated for routine laboratory use [15]. We demonstrated that different TEG assays showed no significant day-to-day variation, and the coefficient of variance (CV) for the TEG parameters investigated was acceptable (5–10%) for clinical practice and when performed on citrated blood samples. Therefore, TEG analyses can be performed in the laboratory and displayed in real-time at the bedside in the operating room, intensive care unit (ICU), or trauma center, thereby enabling early correction of coagulopathy by clinicians.

Anaesthesiologists at our hospital were trained in functional hemostasis and certified in the clinical use of TEG analysis for actively bleeding patients in accordance with a validated treatment algorithm. Furthermore, the blood bank provided an expert in transfusion medicine and functional hemostasis, including TEG, for consultation around the clock.

2.2. Transfusion packages for massively bleeding patients

We hypothesised that the early administration of plasma and platelets might benefit patients presenting with massive blood loss. Consequently, a "transfusion package" encompassing five units of RBCs, five units of FFP and two units of PC, with each PC pooled from four blood donors, was introduced. The blood components were to be administered in parallel via separate intravenous lines, and the administration was to continue until hemostasis was secured. Importantly, the rate of administration of the transfusion package was linked to the rate of bleeding, and pressure was applied to increase the rate of administration

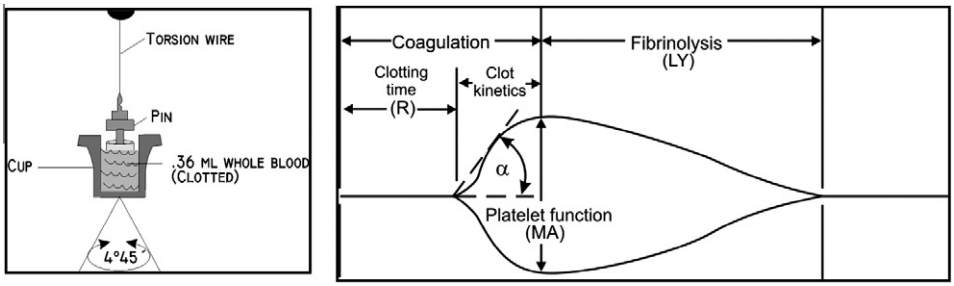

Fig. 1. Thrombelastograph (TEG) technology and measured parameters.