Author’s response to reviews

Title: Assessment of Haemostasis in Patients undergoing Emergent Neurosurgery by Rotational Elastometry and Standard Coagulation Tests: A Prospective Observational Study

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Author’s response to reviews:

Dear Editor,

We thanks the reviewers for raising valuable comments and questions regarding the submitted paper.

This revised version includes all responses to these queries.

We are pretty confident that the paper has been improved and may be of interest to clinicians involved in the care of neurosurgical patients in emergency settings.

Marc Licker

Answers to Reviewer 1

1. Inhomogenous study population.

We fully agree that the study population sample is heterogenous namely regarding the inclusion criteria. The common criterion for study eligibility was that all patients required emergent surgery lasting at least 120 min. These patients presented variable degrees of cerebral impairment consequent to direct brain trauma, intracranial hypertension and/or brain ischemia
associated with intracranial bleeding (epidural hematoma, subarachnoid haemorrhage) and/or intracranial tumor. In contrast with other tissues, the injured brain has the unique ability to trigger the coagulation pathway when even small volumes of tissues are damaged. Leptomeninges contain high concentration of tissue plasminogen activator (tPA) and it has been hypothesized that brain trauma or intracranial tumor/hematoma triggers the local release t-PA resulting in clot dissolution and enhanced bleeding.

In the Introduction section, we underline this point as: “Likewise, intracranial hypertension and brain ischemia in the context of brain hematoma/tumor, have also been shown to initiate the coagulation cascade in non-trauma patients [6,7]. Variable tissue release of thrombin and plasminogen activator, along with activation of the protein C pathway and platelet dysfunction may all concur to these acute hemostatic disorders. Moreover, the efficacy of antifibrinolytic agents in reducing blood loss in the context of brain trauma, subarachnoid hemorrhage and intracranial tumor emphasizes the importance of hyperfibrinolysis in patients undergoing neurosurgical procedures [8-10].”

4 new references have been added:


In the Discussion section (Limitations), we mention: “First, this was a single center study with a relatively small and heterogenous sample of patients with different acute brain disorders, comorbidities and treatments.”

2. 35/92 patients (38%) received anti-platelets and/or anticoagulant therapy. What would happen if these patients were excluded? What is the impact of this therapy?
Actually, some patients were taking more than one antiplatelet/AC drug, so that 27/92 or 29% (instead of 35/92) patients presented with drug-induced hemostatic abnormalities.

Table 1 has been modified.

To analyze the impact of preoperative antiplatelet/anticoagulant treatment on blood transfusion, we performed additional ROC curve analysis by removing from the population sample, sequentially: 1) all patients taking antiplatelet/anticoagulant, 2) only those taking antiplatelet drug and, 3) finally only those taking anticoagulants.

As illustrated in Figure 2, these treatments barely, if not, affected the AUC curve results.

In the Results section, we added: “Removing patients treated preoperatively with anticoagulant and/or antiplatelet drug did not significantly alter the main ROC results, the largest AUC were still achieved for fibrinogen levels (0.71, 95%CI 0.57-0.86), INTEM-MCF (0.74, 95%CI 0.61-0.86) and MCF-FIBTEM (0.75, 95%CI 0.62-0.87).”

Clinicians in charge of these patients were obviously well aware of the effects of the antiplatelet/anticoagulant treatment and, the abnormal bleeding pattern could be corrected or minimized with a targeted hemostatic therapy (e.g., FFP, PCC, thrombopheresis).

This point is further emphasized in the Discussion section as: “Interestingly, preoperative treatment with anticoagulants and antiplatelets did not alter the predictive value of ROTEM-derived parameters for transfusion requirement. This could be explained by the fact that, clinicians being aware of these drug-induced hemostatic effects, administered FFP and/or thrombopheresis to minimize intraoperative bleeding.”

3. Definition of blood loss > 3 RBCs

Observational studies in patients with traumatic brain injury, subarachnoid or intracranial hemorrhage, and hemorrhage have demonstrated that both prolonged anemia and PRBC transfusions were associated with worsened outcomes. The need for PRBCs transfusion is much larger during emergent surgeries than in elective procedure. In a cohort of 547 patients undergoing intracranial aneurysm surgery, Le Roux et al. reported that 134 (22%) required blood transfusion and that aneurysm rupture was associated with the largest PRBCs transfusion (mean of 3.6 unit vs 1.9 units in non-ruptured aneurysms).

In this study, number of transfused PRBCs was used a surrogate of excessive bleeding. Actually, we identified the cut-off value of 3 units PRBCs based on our local data (median value in the database including emergent neurosurgery).
To clarify this important point, we made the following modifications in the manuscript:

- **Study Design:** “This study was performed as a prospective unblinded observational investigation. Intraoperatively, the hemostatic therapy (fresh frozen plasma [FFP], prothrombin complex concentrate [PCC], thrombopheresis, activated factor VII) was guided by the results of SCTs and ROTEM testing as well as by clinical judgement (Fig. 1). This algorithm had been implemented 2 years previously in our department, for all types of major surgery.”

- **Statistical Analysis:** “In our institutional database, we found that 85% of patients undergoing emergent neurosurgical procedures were transfused, the median PRBC transfusion was 3 units and 34% of patients received at least 3 RBCs. Hence, the cohort of patients was divided into two groups, high bleeders (HB) receiving at least 3 PRBCs or requiring re-operation for hematoma drainage and, low bleeders (LB) receiving less than 3 PRBCs and not requiring re-operation for hemostasis. A minimal sample size of 90 patients was deemed necessary to detect this transfusion threshold based on preoperative fibrinogen concentrations (OpenEpi software version 2.3).[16].”

- **Discussion:** “Since small intracranial hematomas or ongoing bleeding may have devastating effects, transfusion of at least 3 PRBCs was used as a surrogate to define major bleeding among our neurosurgical patients.[29-31] This contrasts with cardiac surgery, liver transplantation and multiple trauma where cut-off value for major bleeding are ranging from 4 to 10-PRBCs and are associated with a high burden of morbidity and mortality.[24-26]”

Two references have been added:


4. **Timing of blood drawing seems different for SCT (upon admission) and ROTEM (in the OR)**

This is an important point to underline. In this study, we aimed to compare two diagnostic methods of coagulation disorders (SCTs vs POC-ROTEM) in “real” conditions. When a neurosurgical case is scheduled on the emergency list, the anesthesiologists first rely on all
preoperative results, including SCTs and later, when the patient arrives in the operating room, POC-ROTEM analysis are performed.

To emphasize this issue, we made the following modifications:

Methods: “… For ROTEM analysis, blood was sampled in the operating theater on citrated tubes from the radial arterial catheter with a continuous heparin-free sodium chloride flushing system.”

Discussion (limitations): “Second, the different timings of blood sampling for coagulation testing likely could influence the results but this reflected the practical aspects of managing these critically-ill surgical patients. Indeed, blood for ROTEM analysis was collected later than for SCTs, -after the initiation of fluids resuscitative/stabilization interventions and closer to the start of surgery-, therefore ROTEM parameters might better characterize the ongoing coagulation abnormalities.”

5. Algorithm to guide transfusion and hemostatic therapy

Controversies exist regarding the precise thresholds for guiding transfusion that depend on type of surgery and patient’s comorbidities. So far, evidence-based guidelines regarding blood transfusion in neurosurgery are scarce and therefore, transfusion practices are highly variable and often based on institutional preferences.

In the current study, in agreement with experts in transfusion medicine, patients received PRBCs when the hemoglobin level decreased below 90g/L.

Regarding perioperative hemostatic therapy, a simple algorithm based on ROTEM parameters was already implemented when we started the current study and this algorithm was known by all clinicians working in the department and it was largely applied in major surgery elective and emergency surgery.

In the Method section (patient management):

”Blood losses were substituted in a 2:1 ratio with a balanced crystalloid solution (Ringer-acetate; B. Braun, AB). One or two units of PRBC were administered if the hemoglobin concentration decreased below 90 g/L.”

In the Method section (Study Design):

“Intraoperatively, the hemostatic therapy (fresh frozen plasma [FFP], prothrombin complex concentrate [PCC], thrombopheresis, activated factor VII) was guided by the results of SCTs and ROTEM testing as well as by clinical judgement (Fig. 1). This algorithm had been implemented 2 years before the start of the study in our department, for all types of major surgery.”