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Editorial: RIFAT LATIFI: The First Chapter of the New Book of Kosova College of Surgeons

RUSSELL ANDREWS: The Importance of Surgical Care to Achieve the United Nations Sustainable Development Goal for Healthy Lives by 2030

BELLAL JOSEPH: Breaking the Frailty Code: Emergency General Surgery in the Elderly

DEMETRIUS LITWIN: Hand-Assisted Laparoscopic Living Donor Hepatectomy

LIOR LEVY, ABASS SMILEY, RIFAT LATIFI: Independent Predictors of In-Hospital Mortality in Patients Undergoing Emergency Admission for Arterial Embolism and Thrombosis in the USA: A 10-Year National Dataset

LIOR LEVY, ABBAS SMILEY, RIFAT LATIFI: Mortality in Emergently Admitted Patients with Empyema: An Analysis of 18,033 Patients

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Advances in Trauma Resuscitation

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Abstract
Fortunately, there has been a decrease in mortality from trauma over the last five decades, with a drop of 40% for mortality and a 47.5% decrease in years of potential life lost. Many of these improvements are attributed to advances in the resuscitation of trauma patients (3). This paper reviews advances in trauma resuscitation by assessing transfusion requirements, diagnosis of coagulopathy of trauma, the resurgence of Whole Blood, pre-hospital plasma, coagulation factor replacement, fibrinogen supplementation, tranexamic acid and valproic acid in the trauma service.

Keywords: transfusion, coagulopathy of trauma, Whole Blood, pre-hospital plasma, tranexamic acid and valproic acid

Trauma remains one of the leading causes of death among patients aged 1-46 years. Post-traumatic hemorrhage is the most common preventable cause of early death, with up to a 35% mortality rate.[1] According to the National Academies of Sciences, Engineering, and Medicine (NASEM) report, up to 1 in 5 trauma deaths are preventable, corresponding to an average of 30,000 potentially avoidable deaths from exsanguination in the US.[2] Fortunately, there has been a decrease in mortality from trauma over the last five decades, with a drop of 40% for mortality and a 47.5% decrease in years of potential life lost. Many of these improvements are attributed to advances in the resuscitation of trauma patients.[3]

Severely injured trauma patients tend to present with tissue hypoperfusion and shock due to hemorrhage. Furthermore, every minute delay in hemorrhage control leads to a 7% increase in mortality for severely injured patients. The scenario is worsened by fluid administration, hypothermia, acidosis, and unbalanced coagulation pathway activation culminating in the coagulopathy of trauma (COT). Moore et al. have recently summarized COT, encompassing concepts like COT phenotypes, endothelial and complement systems activation, tPA involvement, and activated protein C.[4] Damage Control Resuscitation (DCR) has emerged as a cornerstone principle for managing severely injured trauma patients and preventing COT. The importance of the DCR principle for managing a trauma patient has been elucidated previously in multiple papers. A review by Cannon et al. highlights the importance of

permissive hypotension, limited crystalloid resuscitation, early hemorrhage control, use of hypertonic saline and other pharmacologic adjuncts to resuscitation, and balanced hemostatic resuscitation as the foundational concepts of DCR.[5,6]

Assessing Transfusion Requirement

The decision to transfuse a patient relies on assessing hemodynamic stability and evaluation of possible ongoing hemorrhage. Multiple studies have evaluated predictive scores for the activation of Massive Transfusion Protocols (MTP).[7,8] The emergence of the Revised Assessment of Bleeding and Transfusion (RABT) score, which includes injury-related variables and clinical assessment, has demonstrated high predictive power for the activation of MTP.

Table 1. RABT Score

Table 1. RABT Score		
Variables	**Yes**	**No**
Positive FAST Exam	1	0
Shock Index >1	1	0
Presence of Pelvic Fracture	1	0
Penetrating Injury	1	0

Diagnosis of Coagulopathy of Trauma

There have been significant advances in the technology used to diagnose COT.[9] Previous laboratory tests used to assess coagulation abnormalities in the trauma patient were limited in practicality, ease of use, and information provided. Also, they were restricted to the in-hospital setting. New technology, such as thromboelastography (TEG) and thromboelastometry (ROTEM), have addressed these limitations, introducing real-time point-of-care assessment in the resuscitation of trauma patients. These new technologies have the advantage of giving a comprehensive assessment of coagulation factors, fibrinolytic factors, and platelets physiology. They are more accurate, faster, portable for pre-hospital settings, and provide feedback and guidance for massive transfusion. In addition, compared to conventional assays, which only look for clot formation, TEG/ROTEM monitor all the phases of the coagulation cascade from the clot formation to its lysis.

Jeger et al. compared the precision of these new technologies, Rapid TEG (a new variant of TEG) and conventional assays to evaluate coagulopathy in patients with multiple injuries. They found that Rapid TEG and TEG/ROTEM were faster in detecting clot formation with reliable information, which could have implications for improving trauma patient care.[11] Evidence has also shown that the use of these new technologies is associated with earlier detection of coagulopathy, decreased 24-hour mortality, lower packed red blood cell (PRBC) and fresh frozen plasma (FFP) transfusion requirements, lower transfusion costs, shorter hospital and ICU length of stay (LOS), and reduced additional invasive hemostatic interventions (angioembolization, endoscopic or surgical procedures).[11-14]

Transfusions in Coagulopathy of Trauma

It has been previously demonstrated that crystalloid administration in trauma patients is associated with worse outcomes, including complications and mortality. In 2015, Holcomb et al. published the evidence from the landmark PROPPR trial. This prospective randomized clinical trial compared outcomes among three cohorts stratified according to their transfusion ratios during resuscitation (FFP: Platelets: PRBC 1:1:1 vs. 1:1:2 vs. local standard of care). They found that a resuscitation ratio of 1:1:1 is associated with improved hemostasis, decreased 24-hours and 30-days mortality, with no difference in complications.[15] These results changed the management of the trauma patient, thus changing the goal to a resuscitation approach to the 1:1:1 ratio, mimicking that of whole blood (WB).

The Resurgence of Whole Blood (WB)

WB was the original and the only means of blood transfusion during the World Wars until up to the 1970s. Afterwards, the military realized the tremendous resources required to support a WB transfusion program and adopted early crystalloid transfusions in an attempt to reduce resource utilization. It was quickly realized though, that this was a mistake, as crystalloid resuscitation was found to be associated with dilutional coagulopathy, compartment syndrome, and systemic

inflammatory complications. However, continuing WB transfusions was difficult as limited storage capabilities meant that too much blood was being wasted. Thus, we developed and switched to component therapy, which allowed for much longer storage times and reduced wastage. Years later, WB is making a resurgence with the advent of modern storage techniques.

WB use has been associated with improved outcomes, compared to component therapy in multiple military and civilian settings.[16-19] There is yet a concern for the limited supplies of Rh-blood products in some blood banks, which prevents implementation and sustainability at many trauma centers. When Rh- whole blood is unavailable, low titer O whole blood appears to be a safe alternative.[20] Seheult et al. found no difference in post-transfusion haptoglobin, creatinine, potassium, or LDH levels among recipients of uncrossmatched, low-titer, group O positive whole blood compared to crossmatched O- in civilian trauma patients.[21]

There is concern about the differences between WB and reconstituted component resuscitation. Kornblith et al. demonstrated that whole blood is associated with increased maximum clot firmness, maximum amplitude at 20 mm, increased product hemoglobin, and platelet count.[21] Likewise, Nessen et al. conveyed that whole blood resuscitation was associated with decreased mortality risk in the military setting.[18] On a larger scale, we assessed nationwide outcomes of using WB and showed that WB, as an adjunct to component therapy, is associated with improved outcomes in the resuscitation of severely injured civilian trauma patients.[23] Recently, even the pre-hospital use of WB has been recommended if the patient is unstable and resources are available.[24]

Pre-hospital Plasma

Along with the use of WB, plasma is an integral component for hemostatic resuscitation in the injured patient. Moore et al. performed a randomized, single-center trial where consecutive trauma patients in hemorrhagic shock were randomly assigned to receive either plasma or normal saline. What they found is that the use of pre-hospital plasma was not associated with survival benefit. Nonetheless, they hypothesized that blood products might be beneficial in settings with longer transport times.[25]

Later, in the PAMPER trial, a multicenter, cluster-randomized phase 3 superiority trial, Sperry et al. aimed to determine the effectiveness and safety of transfusing patients with severe trauma and major bleeding using plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio. Their results displayed that the pre-hospital administration of thawed plasma was safe among patients with severe trauma and major bleeding. It resulted in lower 30-day mortality and a lower median prothrombin-time ratio, compared to standard-care resuscitation.[26]

Coagulation Factor Replacement

As trauma patients lose blood due to exsanguination, they also lose coagulation factors. Moreover, trauma-induced exposure of the thromboplastin-rich subendothelial tissue to flowing blood induces the activation of the coagulation cascade, which may trigger consumptive coagulopathy. That is why these factors must be replaced through adjuncts to resuscitation. One such adjunct is prothrombin complex concentrate, which can be used to rapidly replenish vitamin-K-dependent factors, due to its high concentrations of factors II, VII, IX, and X. PCC needs no thawing, does not require blood group testing and matching, has a low risk for transfusion-related adverse events, and is more effective than FFP in rapidly reducing the International Normalized Ratio (INR) of coagulopathic trauma patients.[27]

We have performed multiple studies on the effects of PCC, used as an adjunct in the resuscitation of trauma patients in a variety of settings, which range from orthopedic trauma to neurotrauma. All of these studies have shown an improvement in patient outcomes, including reduced transfusion requirements, earlier time to INR correction, fewer in-hospital complications, earlier times to surgery, and lower mortality.[28-30] We have also shown that the use of 4-PCC, as an adjunct to WB, is associated with a reduction in transfusion requirements and Intensive Care Unit Length of Stay (ICU LOS) compared with WB alone in the resuscitation of trauma patients.[31]

Fibrinogen Supplementation

Fibrinogen is a unique coagulation factor. It is the most critical downstream endpoint for the coagulation system. Fibrinogen is converted to fibrin by the coagulation system to bind platelets together and make a stronger and more insoluble clot.

Demetriades et al. analyzed a cohort of massively transfused trauma patients and classified them into three

groups according to the fibrinogen level in admission to the surgical intensive care unit (SICU) as: normal (≥180 mg/dL), abnormal (≥101 to <180 mg/dL), and critical (≤100 mg/dL). They concluded that a fibrinogen level ≤100 mg/dL was a strong independent risk factor for death among these patients.[32]

Fibrinogen supplementation can be achieved by the use of FFP or Coagulation Factor Concentrates (CFC) such as fibrinogen concentrate or cryoprecipitate. Petra et al. conducted a single-center randomized controlled trial including all severely injured adult trauma patients with COT diagnosed by ROTEM. The study had to be concluded early because of the high proportion of patients in the FFP group that required rescue therapy compared with those in the Coagulation Factor Concentrate (CFC) group. Those treated with CFC had lower rates of Multiorgan Failure (MOF), decreased need for massive transfusion, and a reduced requirement for rescue therapy.[33]

There was still need for evidence regarding pre-hospital fibrinogen usage. Ziegler et al. conducted a clinical trial, evaluating the effects of fibrinogen supplementation in the pre-hospital setting among severely injured trauma patients. After analyzing the outcomes, they found an increased maximum clot firmness and median fibrinogen concentration.[34] Multiple trials are being conducted to further clarify the impact of fibrinogen supplementation in the trauma patient.

Tranexamic Acid and the Injured Patient

Tranexamic acid (TXA) is an adjunct to massive transfusion resuscitation. Data suggest better outcomes in patients who received it during the pre-hospital period. It is an inexpensive drug and works by blocking the activation of plasminogen into active plasmin, thus preventing the breakdown of clots and hyperfibrinolysis.

Brohi et al. concluded that increased fibrinolysis is attributed to over-degradation of Plasminogen Activator Inhibitor (PAI) by activated C proteins (aCP), thus resulting in increased levels of active tissue Plasminogen Activator. However, Moore et al. assessed COT using TEG and demonstrated that it is not the over-degradation of PAI, but rather the over-release of tPA that is responsible for hyperfibrinolysis.

Multiple studies have addressed the role of tranexamic acid in traumatic brain injury (TBI) patients. These studies stated that several conditions limit the benefit of tranexamic acid (which should be administered within 3 hours of presentation, only in mild-moderate TBI). However, the evidence shows that there is a decrease in deaths from bleeding among mild to moderate TBI patients.[35-38]

In the pre-hospital setting, the landmark STAAMP trial on the effects of pre-hospital TXA administration in trauma patients at risk for hemorrhage was conducted. It was double-blinded and assessed seizure rates as well as VTE complications. Varied dosing regimens of TXA were evaluated. The results showed that there is a survival benefit of TXA in specific subgroups of patients (those who received a higher dose of TXA, those who received TXA within 1 hour of injury, and those with severe hypotension).[39] Additionally, secondary analysis of the STAAMP trial data showed decreased MOF rate and reduced 24-hours transfusion requirements.[40]

Valproic Acid in the Trauma Service

Valproic acid is an antiepileptic drug that exhibits its pharmacologic effects in a couple of ways, such as by acting on GABA (γ aminobutyric acid) levels in the CNS, blocking voltage-gated ion channels, and inhibiting histone deacetylase.[41] Its role in the injured patient is being clarified by emerging evidence, which shows a possible decrease in trauma-induced apoptosis, platelet dysfunction, and a possible neuroprotective effect.[42,43] Multiple clinical trials are undergoing to explain this hypothesis.

Conflict of Interest Disclosure Statement

The author has no conflicts of interest to disclose.

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