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Opinion

Dealing with Traumatic Coagulopathy: A Long Way to Go

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Major trauma with hemorrhage is a leading cause of morbidity and mortality accounting for 40% of deaths (1). Development of coagulopathy further increases trauma mortality emphasizing that coagulopathy is a key target in the phase of bleeding (2). Over the recent decade, many investigators made an active effort to find the pathogenesis of traumatic coagulopathy, and found that one of four patients who arrived in the emergency department after trauma was in the state of traumatic coagulopathy already (3). The new terminology, acute traumatic coagulopathy (ATC) was created. ATC is endogenous clotting dysfunction occurring immediately after massive trauma when shock, hypoperfusion and vascular damage are present (4). It has been demonstrated in traumatic patients who received little or no intravenous fluid therapy negating the long-held belief that iatrogenic hemodilution is the main causative factor in traumatic coagulopathy (5). Mechanisms for ATC include activation of protein C, endothelial glycocalyx disruption, depletion of fibrinogen, and platelet dysfunction (4), of which activated protein C-associated fibrinolysis and fibrinogenolysis predominate (1). It afflicts up to 30% of severely injured adults (6) and 60% of children and adolescents (7), signaling an increased likelihood of all-cause and hemorrhage-associated mortality (6).

Hemostatic resuscitation aiming at controlling coagulopathy has proved to be associated with improved survival and becomes the mainstay of trauma resuscitation (2). The Task Force for Advanced Bleeding Care in Trauma which comprises a multidisciplinary team of pan-European experts representing the fields of emergency medicine, surgery, anesthesiology, hematology and intensive care medicine, was founded in 2004 with aims of developing guidelines and improving strategies to treat polytraumatic patients. The original guideline for the management of bleeding trauma patient was published in Critical Care in 2007 (8), and updated in 2010 (9), 2013 (10) and 2016 (11). Over the last 10 years, clinical management has been changed from maintaining an adequate circulating volume and oxygen carrying capacity first, then dealing with coagulopathy to hemostatic resuscitation as early as possible (5). In the recent publication, Rossaint and colleagues presented 39 recommendations on initial resuscitation and prevention of further bleeding, diagnosis and monitoring of bleeding, tissue oxygenation, type of fluid and temperature management, rapid control of bleeding, initial management of bleeding coagulopathy, further resuscitation and guideline implementation and quality control (11).

Coagulation management is the highlight and major chapter of this guideline, and reflects the newest opinions and results of scientific researches. They recommended that monitoring and measures to support coagulation be initiated immediately upon hospital admission (Grade 1B) (11), and tranexamic acid administered as early as possible (Grade 1A). The latter has been proved to reduce the risk of death due to bleeding by 0.8% and led to a reduction in bleeding deaths by one- third, mainly through preventing exsanguination within the first 24 h (11), in accordance with that fibrinolysis is the main mechanism of ATC (1).

To facilitate goal-directed therapy, different strategic approaches about hemostatic resuscitation were recommended depending on the availability of rapid point-of- care coagulation testing. The use of plasma and erythrocytes in a ratio of at least 1:2 in initial resuscitation (Grade 1B) was recommended when standard laboratory coagulation values were available, and further plasma

transfusion depended on PT and APTT (11). If viscoelastic tests were available, fibrinogen concentrate and erythrocytes were recommended in the initial management of coagulopathy (Grade 1C), and retreatment with fibrinogen concentrate or cryoprecipitate was recommended if significant bleeding was accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5～2.0 g/L (Grade 1C) (11). Platelets were recommended when a platelet count less than 50 × 109/L (Grade 1C) (11). They also suggested managements for patients pre- treated with antiplatelet agents or anticoagulants (11).

After carefully reading this guideline, we believe that these recommendations were based on scientific evidences and can guide clinical practice to improve treatments for traumatic patients. Before it is adopted into clinical practice, however, we have some confusions about it (Table).

Firstly, if viscoelastic tests were available, they recommended a fibrinogen concentrate-based strategy (Grade 1C), and suggested prothrombin complex concentrate (PCC) or plasma for patients with delayed coagulation initiation and normal fibrinogen levels (Grade 2C) (11). It seems that we could choose fibrinogen and PCC without plasma when using viscoelastic tests. But we all know that fibrinogen and PCC are not equivalent to plasma, as they do not contain important proteins such as factors V, XII and XIII (12). Kunitake and his colleagues proved the crucial association of factors V and VIII on mortality following trauma (13). So fresh frozen plasma might be helpful for traumatic patients as it contains them. If we want to choose plasma for traumatic patients, a prolonged "reaction time" using viscoelastic tests might be the indication, but the scientific evidence is scarce (11). All grades of recommendations based on the viscoelastic tests in the chapter of coagulation resuscitation are grade C. It means that all evidences of those are low quality and the recommendations may change when there is higher quality evidence. When coagulation resuscitation for traumatic patients is guided by viscoelastic tests, the value of plasma remains more clinical trials.

Secondly, the suggestions of managements for patients pre-treated with antiplatelet agents or anticoagulants were based on the knowledge that which agent the patient was pre- treated with had been known. In China, it is difficult to get the medical history if the patient cannot talk. When facing a critically injured patient with coagulopathy, we can't distinguish whether the patient has taken pre- injury antiplatelet or anticoagulation or not only by coagulation monitoring, as both of them can present coagulation dysfunction. Ali et al. reported that thromboelastogram did not detect pre- injury anticoagulation in acute trauma (14). The abnormal results from present laboratory tests reflect the patient's current condition only, and can't tell us the reasons of them. Moreover, viscoelastic hemostatic tests still have some limitations. Platelet inhibition or dysfunction may not be identified with the standard viscoelastic hemostatic assays, thromboelastogram results might be normal in patients receiving warfarin, and capacity of thromboelastogram to detect new oral anticoagulants remains to be determined in vivo (12). In addition, most of references in this section were not about traumatic patients. Then we think that these suggestions on dealing with patients pre-treated with antiplatelet agents or anticoagulants maybe are more suitable for those undergoing selective surgery in China. How to use present monitoring to detect pre- injury anticoagulation and then guide management of traumatic coagulopathy is still a clinical difficulty.

Finally, it has been well known that pulmonary embolism (PE) is a leading cause of delayed mortality in patients with severe injury (15). In this guideline, pharmacological thromboprophylaxis was recommended within 24 h after bleeding has been controlled (Grade 1B) (11). However, which agent should we choose and what dosage is optimal didn't be recommended. Byrne and colleagues reported that thromboprophylaxis with low- molecular-weight heparin (LMWH) (vs. unfractionated heparin) was associated with significantly lower risk of PE, and trauma centers favoring LMWH- based prophylaxis strategies reported lower rates of PE. They suggested LMWH should be the anticoagulant agent of choice for prevention of PE in patients with major trauma (14). Despite LMWH administration, some patients still have venous thromboembolism (VTE) or PE (16,17). This suggests that the routine dosage to prevent VTE in patients with high risk

Table. The authors' Confusions about the European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma: Fourth Edition.

Viscoelastic tests guided coagulation resuscitation	Patients pre-treated with antiplatelet agents or anticoagulants	Thromboprophylaxis
• Fibrinogen and prothrombin complex concentrate are not equivalent to plasma. • A prolonged "reaction time" using viscoelastic tests might be the indication for the administration of fresh frozen plasma, but there is no high quality evidence. • All evidences in this chapter are low quality. • The value of viscoelastic tests guided administration of plasma remains more clinical trails.	• The abnormal results from present laboratory tests can't tell us the reasons of them, unless the medical history has been known. • Viscoelastic hemostatic tests still have some limitations. • Most of references in this section were not about traumatic patients. • These suggestions maybe are more suitable for those undergoing selective surgery in China.	• Low- molecular- weight heparin might be superior than others in pharmacological thromboprophylaxis. • An adjusted dosage may be better than a fixed dosage, such as anti-Xa-guided enoxaparin dosing. • A longer period of thromboprophylaxis may be necessary for some traumatic patients.

should be reconsidered and an adjusted dosage may be better than a fixed dosage (16). Anti-Xa-guided enoxaparin dosing was reported to reduce the incidence of VTE from 7.6% to 1.1% after trauma (18) and the rate of deep vein thrombosis (DVT) from 20.5% to 7.1% in high-risk trauma patients (19). How long should a course of thromboprophylaxis be is not clear yet. Alabed et al. reported a PE incidence of 0.5%～6.0% and DVT incidence of 2.0%～8.0% 3～6 months following spinal cord injury. This suggested that a longer period of thromboprophylaxis may be necessary for some traumatic patients (20).

In conclusion, traumatic coagulopathy is a complicated pathophysiological process. The management of traumatic coagulopathy should cover the whole process from pre- hospital to after discharge. The recommendations on management of coagulopathy following trauma in this guideline are practical, but there are still many circumstances we don't know how to deal with. To manage traumatic coagulopathy, we believe that there is still a long way to go.

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