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Review Article

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Nano- and micro-materials in the treatment of internal bleeding and uncontrolled hemorrhage

Elizabeth Gaston, BSc[a,b], John F. Fraser, PhD[c], Zhi Ping Xu, PhD[a], Hang T. Ta, PhD[a,*]

[a]*Australian Institute for Bioengineering and Nanotechnology, the University of Queensland, Brisbane, QLD, Australia*
[b]*Department of Bioengineering, Clemson University, Clemson, SC, USA*
[c]*Faculty of Medicine, Critical Care Research Group, Prince Charles Hospital and the University of Queensland, Brisbane, Brisbane, QLD, Australia*

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Abstract

Internal bleeding is defined as the loss of blood that occurs inside of a body cavity. After a traumatic injury, hemorrhage accounts for over 35% of pre-hospital deaths and 40% of deaths within the first 24 hours. Coagulopathy, a disorder in which the blood is not able to properly form clots, typically develops after traumatic injury and results in a higher rate of mortality. The current methods to treat internal bleeding and coagulopathy are inadequate due to the requirement of extensive medical equipment that is typically not available at the site of injury. To discover a potential route for future research, several current and novel treatment methods have been reviewed and analyzed. The aim of investigating different potential treatment options is to expand available knowledge, while also call attention to the importance of research in the field of treatment for internal bleeding and hemorrhage due to trauma.

Key words: Nanomaterials; Internal bleeding; Hemorrhage; Coagulopathy; Trauma

Severe bleeding accounts for approximately one third of total deaths in hospitals that occur due to trauma events.[1] Hemorrhage is the primary cause of preventable military death and the second cause of civilian trauma deaths.[2] Studies indicate that the majority of injury mortality during civilian and military trauma occurs in the prehospital period, defined as the time between injury and admission to the hospital.[3] Current protocol for the treatment of internal bleeding relies on the usage of extensive medical equipment such as computed tomography scanners, tests to monitor coagulation, and in some cases, surgical tools.[4] The absence of an effective, safe, and quick treatment method results in preventable deaths during the pre-hospital and clinical phases. While on the battlefield, there is little to no standard protocol established for the treatment of internal bleeding and hemorrhage. Unlike external injuries, internal injuries cannot be treated by compression and thus intravenously administered treatment to induce coagulation and halt bleeding would be ideal. In areas where medical equipment is not readily available, quick and effective drugs are necessarily administered intravenously on the site of injury. There are many complications to consider when developing a solution which induces coagulation due to the harmful side effects to excessive blood clotting, such as pulmonary embolism and deep vein thrombosis.[5] In order to design a safe and effective means of treatment for internal bleeding and hemorrhage, it is necessary to summarize and understand current innovations and options available. This review article aims to provide an overview of current and potential treatment options of internal bleeding and hemorrhage in both clinical and pre-hospital phases. Many studies on the use of nano/micro-materials as hemostatic agents have been conducted[6-21] and several researchers in this field have come to the conclusion that nano/micro-materials would be useful in the detection and maintenance of internal bleeding and hemorrhage.

Coagulation

Thrombohemorrhagic balance is maintained in the body by interactions between coagulation and the fibrinolytic system.[22] Primary hemostasis is defined as the process where platelets

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*Corresponding author at: The University of Queensland, Brisbane, QLD 4072, Australia.
E-mail addresses: h.ta@uq.edu.au, hangthuta@gmail.com (H.T. Ta).

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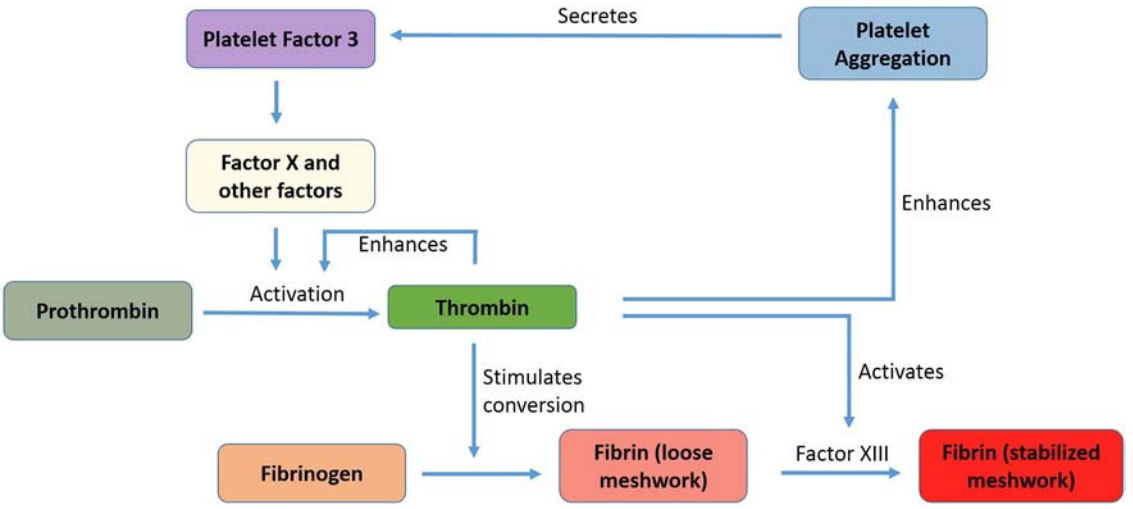

Figure 1. Coagulation cascade. Following injury to the blood vessel, platelets are activated, aggregated and form platelet plug on top of the injury. Activated platelets then trigger the release of clotting factors that activate prothrombin to thrombin. Thrombin converts soluble fibrinogens to non-soluble fibrins that form fibrin meshwork on top of the platelet plug. Factor XIII is activated by thrombin and stabilizes the fibrin meshwork. The clot typically appears red due to the entrapment of red blood cells in the fibrin meshwork.

interact with parts of a damaged vessel wall, which leads to the formation of a platelet plug.[23] To initiate platelet adhesion, fibrinogen and Von Willebrand factor must be present. Once platelets adhere to the injury site, they are activated due to their exposure to the damaged endothelium and vessel wall.[23] Thrombin plays a role in the activation of platelets, regulation of factors important for coagulation, and the cleavage of proteins necessary to form blood clots.[24] Upon activation, blood platelets aggregate, leading to the formation of a platelet plug, which temporarily seals off the vascular injury.[23] Thrombin cleaves fibrinogen to fibrin, which forms the mesh of the clot, and also activates factor XIII which regulates the cross-linking of fibrin and thus can improve the strength of a clot.[24] The coagulation cascade has been illustrated in Figure 1 shown below. Maintaining hemostasis is one of the most important aspects to consider during the treatment of internal bleeding and hemorrhage.

Diagnosis

Symptoms of shock include tachycardia, hypotension and evidence of end organ hypo-perfusion.[25] Focused abdominal sonography for trauma (FAST), Computed tomography (CT) scanners, and angiography are typically used to find the source of the bleed.[4] CT scanning has been an established method of the detection and location of internal bleeds and gives information necessary to determine whether surgical intervention or angiographic intervention is needed.[26] CT scans are quick and highly accurate but pose several major problems such as steep costs, high doses of radiation, and the chance for data misinterpretation.[27] Recently, there has been much enthusiasm toward the use of focused abdominal sonography for trauma due to the ability to scan in the emergency/ICU department, its efficacy and immediate result.[28]

Along with the detection and location of an internal bleed, it is important for tests to be performed to ensure blood products remain at equilibrium.[29] Prothrombin time and activated partial thromboplastin time are typical factors to be evaluated in effort to monitor hemostasis, the physiological process that stops bleeding at the site of an injury.[30] In order to evaluate these factors, viscoelastical haemostatic assays (VHAs) such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are used in standard protocol.[31] VHAs measure the changes in elastic properties of whole blood during the process of clot formation and breakdown.[30] The factors measured are defined in Table 1.[32] TEG and ROTEM are similar in that they measure physical properties of blood clot strength, such as maximal amplitude and shear elastic modulus, to determine haemostatic status of patients, but differ in hardware used to hold the blood sample.[33] It is important to note that TEG and ROTEM cannot be used to measure platelet inhibition in patients who use aspirin and adenosine 5′-diphosphate receptor inhibitors such as clopidogrel, effient, or ticagrelor. In this case, TEG platelet mapping assays or the multiple electrode impedance aggregometer multiplate must be used.[34]

Pathophysiology

Coagulopathy, or a condition where the blood is unable to properly form clots, commonly develops in trauma situations due to acidosis, hypothermia, and loss of coagulation factors, and is typically associated with poor outcomes and an increase in mortality rate.[35] The disruption of equilibrium of blood clotting factors caused by trauma is associated with the development of acute traumatic coagulopathy (ATC), and in some cases can result in a 4-fold increase in mortality.[36] Fibrinogen, which is cleaved into fibrin to produce blood clots, proves to be one of the most important factors to consider during treatment of ATC and is usually the first factor to drop below reference values during