Common Coagulation Disorders That May Arise Intraoperatively: Specifically DIC

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Neurosurgical patients could have preexisting congenital or acquired systemic coagulation disorders that can complicate their intraoperative management. Further conditions like traumatic brain injury, major trauma, sepsis, and malignancy can cause coagulopathy complicating the course of the neurosurgical patient. Antithrombotic therapy for preexisting conditions adds to the complexity of the situation either exacerbating bleeding or by delaying the surgical procedure. Similarly there are disorders of coagulation that could occur in the postoperative period, one of which is the increased risk of thrombosis in the neurosurgical patients. All of the above-mentioned disorders have been dealt with in detail in other sections of this textbook. The most important coagulation disorder that may arise intraoperatively is disseminated intravascular coagulation (DIC).

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Disseminated Intravascular Coagulation

Introduction

The hemostatic response is tightly regulated so that there is effective control of bleeding at the site of local injury. The platelets, von Willebrand factor, coagulation factors, naturally occurring anticoagulants, fibrinolytic system, and endothelium work in a meticulous fashion to result in a controlled hemostatic response. Disseminated intravascular coagulation (DIC) is the result of a pathological overstimulation of the hemostatic pathway that could present as a simultaneous hemorrhagic and thrombotic process [1]. An individual patient can be either at the thrombotic or at the hemorrhagic end of the spectrum at any given point of time. DIC increases the mortality in trauma patients [2]. DIC is a highly heterogeneous condition with different phases and varying degrees of severity. In 2001 the International Society of Thrombosis and Hemostasis defined DIC as "an acquired syndrome characterized by the intravascular activation of coagulation without a specific localization and arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction [3]."

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Clinical Manifestations

The clinical presentation of DIC could be acute or chronic and the severity can range from mild to severe. DIC can be mild in some presentations that it may be identified only on laboratory testing without any overt clinical symptoms or signs. In the more severe and acute forms there is activation of the coagulation cascade resulting in the formation of micro- and macrovascular thrombosis followed by fibrinolysis of the microthrombi resulting in the increase of fibrin degradation products. Severe DIC can result in thrombosis in the vascular beds of almost all organ systems. There is evidence of microangiopathic hemolytic anemia due to fragmentation of red blood cells as they pass through the microvasculature laden with thrombi. Some of the clinical manifestations of these widespread microthrombi include acute renal failure, respiratory distress syndrome, dermal necrosis, and altered mental status.

The uncontrolled activation of the coagulation cascade also results in the consumption of the clotting factors and platelets. The above process combined with fibrinolysis can result in hemorrhagic manifestations in multiple organs. There can be widespread mucocutaneous bleeding, hematuria, bleeding from central and peripheral venous catheter sites, and intracerebral bleeding. Bleeding into the adrenal glands can result in adrenal cortical failure.

In summary the neurological manifestations in DIC can include thrombotic and hemorrhagic strokes, altered mental status, coma, and convulsions.

Pathophysiology of DIC

Tissue factor (TF) plays an important role in the initiation of DIC in neurosurgical procedures [4]. Brain tissue and tumors are rich in tissue factor and manipulation of the tissues during procedures can initiate DIC medicated by TF. Decreased levels of naturally occurring anticoagulants, like Antithrombin, Protein C, and Tissue factor pathway inhibitor, can exacerbate DIC [5]. Patients could have lower levels of these anticoagulants due to consumption in the clotting process. Plasmin is the key enzyme involved in fibrinolysis. As thrombin generated by the tissue factor initiated clotting process converts the fibrinogen to fibrin, plasmin breaks down the fibrin clot. The balance between the thrombin and plasmin levels determines the clinical phenotype of DIC which can range from extensive thrombosis to overt bleeding.

Laboratory Parameters in DIC

There is no single test or a set of tests that can accurately diagnose DIC. All laboratory testing should be combined with the clinical scenario to help with a diagnosis and management of DIC. Some of the tests that are routinely performed and readily available are prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, fibrinogen, and d-dimer. D-dimer is a cross-linked fibrin degradation product. PT, aPTT, platelet count, and fibrinogen are usually low in moderate to severe DIC with an elevated d-dimer. There are numerous confounding variables in the interpretation of the above-mentioned tests. The coagulation parameters in a patient with liver disease may be similar to a patient in DIC. Factor VIII is synthesized in the endothelial cells whereas all the other factors are synthesized by the liver parenchyma. Getting Factor II, V, X, and VIII levels may help to distinguish coagulopathy of liver disease from DIC. Factor VIII is usually normal or high in early to mid stages of liver failure with the other factors being low. Since DIC is a process where all factors are consumed in the clotting process even Factor VIII is low. Fibrinogen is an acute phase reactant and the levels of the protein may be high in infections and inflammation. So it is important to follow serial levels to evaluate for a decrease in the fibrinogen level due to consumption rather than a one-time test looking for a below normal value. Similarly there are other conditions that can result in a high D-dimer level apart from DIC. Evaluation of the peripheral blood smear by a hematologist may demonstrate red cell fragments and decreased platelet count.

The schistocytes in DIC are not markedly elevated unlike other microangiopathic hemolytic anemias and schistocytes are not required for making a diagnosis of DIC.

Tests like thrombin-antithrombin complexes, soluble fibrin, and prothrombin fragment 1.2 are better than the standard tests discussed previously in the evaluation of DIC. Since these tests are not readily available in most hospitals, their use in the real-time management of DIC is limited.

Assays of global hemostasis are being used commonly during cardiac and hepatic surgeries. These points of care (POC) devices could give an overview of the entire coagulation system including the platelet-clot interaction and fibrinolysis. This is in stark contrast to the commonly performed tests that only evaluate a particular aspect of the clotting cascade. Further these POC devices can be used in the operating room helping with real-time management decisions. Devices like thromboelastogram (TEG), rotational thromboelastometry (ROTEM), and thrombin generation assay (TGA) could aid in the management of DIC during neurosurgical procedures [6]. Unlike the conventional tests these POC devices may help in the early diagnosis of DIC and also inform the surgeon if the patient is in the hypercoagulable phase or hyperfibrinolytic phase of DIC.

DIC Development During Neurosurgical Procedures

DIC can occur intraoperatively during resection of brain tumors or with excessive use of hemostatic products like prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rVIIa).

Resection of Tumors

Neurosurgical procedures for brain tumors can be complicated by the development of DIC. DIC in this setting increases the mortality rate for the patient. Surgical resection of meningioma, oligodendroglioma, neuroblastoma, glioblastoma multiforme, and metastatic adenocarcinoma has been reported in the literature to be complicated by DIC [7]. Rarely DIC can develop after embolization of brain tumors [8].

DIC in the above-mentioned neurosurgical procedures was predominantly hemorrhagic in nature. DIC was caused by the intraoperative manipulation of the tumor. Apart from supportive transfusion therapy with platelets, plasma, and cryoprecipitate, resection of the tumor was important for control of DIC. Tissue factor released from the intraoperative manipulation of meningiomas could have contributed to DIC in this setting. Meningiomas associated with a hemorrhagic complication stained positive for tissue factor by immunohistochemistry compared to meningiomas without hemorrhagic complications [9].

DIC with the Use of Hemostatic Therapy

Neurosurgeons are in situations where complex surgical procedures are needed in patients with congenital or acquired clotting factor deficiencies with inhibitors and these surgeries are usually performed under the cover of inhibitor bypassing agents like prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rVIIa). Similarly the above-mentioned hemostatic agents are used in patients who present with life-threatening intracranial hemorrhage due to supratherapeutic INR on warfarin or target-specific anticoagulants (Rivaroxaban, Apixaban, Edoxaban, and Dabigatran). These hemostatic agents in large doses can result in DIC. PCCs can either be non-activated (containing factor II, VII, IX, and X) or activated (aPCCs—containing factors IIa, VIIa, IXa, and Xa). The non-activated PCCs have a lower incidence of DIC than the aPCCs. It is very important to monitor the patient closely for any symptoms and signs of DIC and laboratory parameters of DIC while receiving systemic hemostatic treatments.

Treatment of DIC

The most important step in the management of DIC is to treat the underlying cause of DIC. The patient has to be supported aggressively with blood product replacement therapy and pharmacological agents depending on whether the patient has bleeding or thrombotic manifestations of DIC. The supportive management plays a crucial role when DIC develops during a neurosurgical procedure for a tumor. The patient will need replacement therapy if there is evidence of bleeding with abnormal DIC labs or if the patient requires a procedure. Cryoprecipitate is used as a replacement for low fibrinogen. Fresh frozen plasma is used for factor replacement if PT and PTT are prolonged despite correcting the fibrinogen. Unactivated prothrombin complex concentrates may be used in conjunction with small doses of FFP if there are volume overload issues. Platelet transfusions are recommended (goal platelet count of >100,000/μl) in a bleeding neurosurgical patient with DIC. When patient has excessive fibrinolysis the use of anti-fibrinolytic agents in the form of lysine analogues (EACA or tranexamic acid) can be considered. Rarely despite the use of the replacement therapy the DIC may be so severe that it is difficult to maintain the coagulation factor levels and fibrinogen at hemostatic levels. In this situation low-dose infusion of heparin at 500 units/h can be considered along with the appropriate factor replacement therapy.

In patients with the thrombotic spectrum of DIC, therapeutic heparin infusion is the recommended treatment of choice.

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