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Diagnosis and Management of Dissemine Intravascular Coagulation

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Review

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ABSTRACT

The primary objective of this review is to define disseminated intravascular coagulation (DIC), which is a complication associated with a range of traumatic and non-traumatic conditions, and to provide insights into its underlying pathophysiology. Additionally, this review aims to emphasise the importance of early recognition of DIC, particularly in cases of thrombotic or haemorrhagic complications, and to highlight the benefits of prompt anticoagulant, blood product, and cryoprecipitate treatment in improving prognosis.

Keywords: Dissemine intravascular coagulation, Thrombosis, Coagulation, Bleeding

Dissemine İntravasküler Koagulasyonun Tanı ve Yönetimi

Derleme

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ÖZET

Bu derlemedeki öncelikli olarak amacımız birçok travmatik veya nontravmatik hastalıklara eşlik eden ve mortaliteyi arttıran dissemine intravasküler koagulasyonu tanımlayarak patofizyolojisi hakkında bilgi verip, erken dönemde tanınmasını sağlamak. Trombotik veya kanamalar ile seyreden dissemine intravasküler koagulasyonun erken dönemde tanınması antikoagulan veya kan ürünleri ve kriyopresipitat tedavisinin erken başlanması prognozu olumlu etkilemektedir.

Anahtar Kelimeler: Dissemine intravasküler koagulasyon, Tromboz, Koagulasyon, Kanama

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Introduction

The initial account of disseminated intravascular coagulation (DIC) was documented by Dupuy in 1834. He observed that animals died immediately following the intravenous administration of brain material and that autopsies revealed the presence of widespread intravascular clots.[1] Thirty years later, Trousseau identified a predisposition to thrombosis in advanced cancer patients.[2] In 1873, Naunyn demonstrated that intravascular clots frequently formed following the intravenous administration of a solution containing erythrocytes, and Wooldridge demonstrated that procoagulant factors were located in erythrocytes.[3–5] A definitive description and pathogenesis of DIC was made in 1955 by Ratnoff et al. in pregnant women and fetuses, who died as a result of amniotic fluid embolism. In 1961, Lasch and colleagues provided the first comprehensive explanation of how DIC might result in bleeding. Their work introduced the concept of consumptive coagulopathy, which remains a fundamental tenet of modern understanding of this condition.[6,7]

The International Society of Thrombosis and Haemostasis defined DIC as " a pathological process involving the systemic activation of the blood coagulation cascade, that ultimately results in microvascular thrombosis and simultaneous depletion of platelets and clotting factors, resulting in life-threatening bleeding".[8] Disseminated intravascular coagulation is observed in approximately 1% of patients admitted to hospital.[9] The incidence rate can be increased according to the underlying conditions. In the oncology population, the estimated incidence was 6.8% in patients with solid tumors, and 83% in patients with sepsis.[10,11]

Etiology and Classification

DIC is typically a secondary complication of underlying diseases. The primary causes of DIC are diverse and include infections, solid tumours, haematologic neoplasms, pregnancy, vascular disease, neonatal pathologies, traumatic or non-traumatic internal-external tissue damage, and chemical or biological agents.[12] Acute promyelocytic leukaemia is the most prevalent neoplastic disease seen in DIC.[13] Mucin-producing tumours, including stomach, ovary and pancreas cancers, play an important role in the development of DIC through the secretion of enzymes or necrotic tissue that can stimulate the coagulation cascade.[14] The emergence of cytokine release syndrome as an adverse event associated with the use of chimeric antigen receptor T cells for the treatment of haematological malignancies such as leukaemia or lymphoma has also been associated with DIC. It is hypothesised that procoagulant factors released as a consequence of endothelial inflammation are the underlying cause of DIC in this patient group. The likelihood of a patient developing DIC is directly correlated with the severity of cytokine release syndrome.[15]

Pathophysiology

Part In simple terms, the pathophysiology of DIC can be described as follows: depending on the underlying disease, procoagulant activation is so strong that a surplus of thrombin exerts excessive influence on anticoagulant regulatory mechanisms, such as protein C, antithrombin, and tissue factor pathway inhibitor, thereby overwhelming their capacity to maintain control. This permits the formation of thrombosis to occur at any point along the vessels.[16] In DIC, there is an inherent conflict between a heightened thrombin state, which clinically presents as microvascular occlusion by thrombosis, emboli, and fibrin thrombi, leading to a gradual failure of multiple organ systems from tissue ischaemia, and a haemorrhagic state can result due to the use of platelet and clotting factor, and/or accelerated plasmin generation.[17] Laboratory abnormalities in this condition, which can be described as 'consumption coagulopathy', include prolonged aPTT and PT/INR, decreased platelets and fibrinogen, and increased fibrin degradation products.

Acute Disseminated Intravascular Coagulation

Acute DIC is a condition characterised by consumptive coagulopathy, whereby the production of thrombin exceeds the natural anticoagulants levels in plasma. It is typically triggered by a significant release of tissue factor into the intravascular space, resulting in the widespread deposition of fibrin thrombi within small vessels. The subsequent is the development of multi-organ dysfunction. Multi-organ failure most commonly affects the lungs and kidneys. Other common sites included are the brain, heart, liver, spleen, adrenal glands, pancreas and gastrointestinal tract.[18,19]

Procoagulant effects of Thrombin (Figure 1):

1. Conversion of fibrinogen to fibrin
2. Activation of factors V, VIII and XI to promote further thrombin generation
3. Activation of factor XIII to promote fibrin cross-linking
4. Thrombocyte aggregation, which induces the clotting system to produce more thrombin.

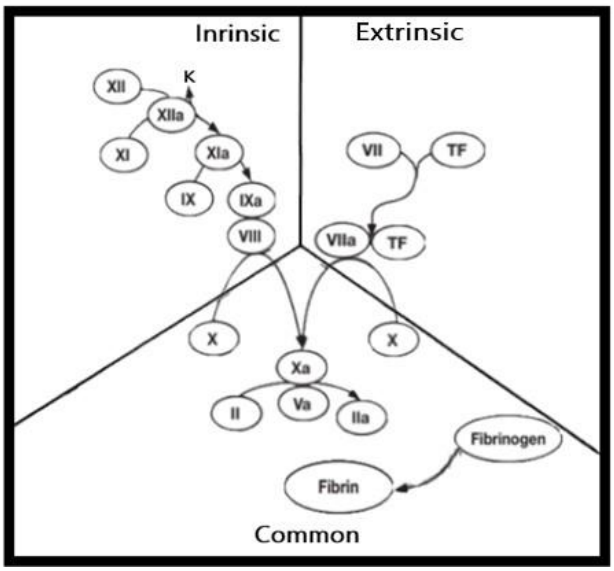

Figure 1. Coagulation cascade pathways

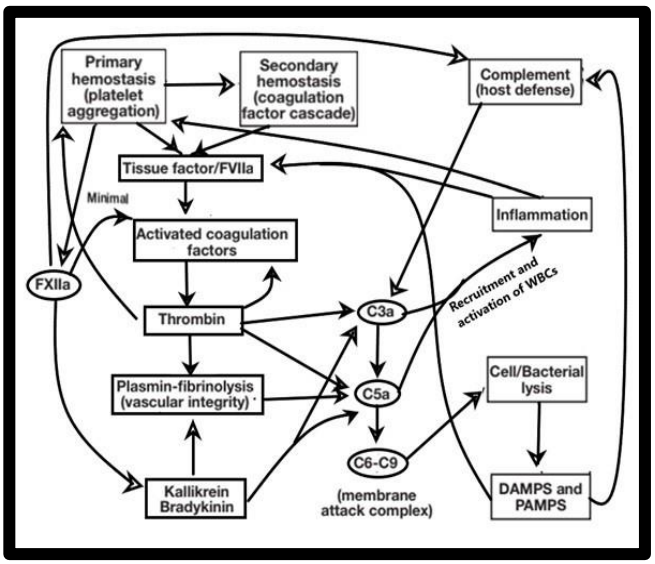

Figure 2. Primary, secondary hemostasis and response of complement system

The effects of thrombin result in the further activation of clotting factors, thereby producing an increased level of thrombin and, consequently, a greater number of fibrin clots. This fibrin thrombus are degraded by plasmin and are converted to fibrin degradation products. When present within the intravascular space, these fibrin degradation products have the potential to interact with the glycoprotein IIb/IIIa receptor, which is located on the surface of thrombocyte and fibrinogen, thereby inhibiting the polymerisation of fibrin and the aggregation of platelets.[17]

The fibrin degradation products, contribute to bleeding, the most common symptom observed in acute DIC, together with the consumption of platelets, fibrinogen and coagulation factors. Other conditions induced by thrombin increase the activity of the coagulation cascade. Thrombin stimulates protease-activated receptors on platelets and increases the intracellular interleukins (IL-1 and IL-6). Their release further enhances proinflammatory activity by increasing thrombocyte activation and leukocyte adherence.[13]

Thrombin is responsible for the release of plasminogen activator inhibitor-1 from endothelial cells and the subsequent activation of thrombin-activatable fibrinolysis inhibitor within the plasma. This ultimately results in a reduction in plasmin-mediated clot lysis. Additionally, DIC results in the decrease of antithrombin and the down-regulation of the Protein C system, thereby reducing the body's capacity to eliminate thrombin. Following the onset of multiorgan failure, the production of anti-thrombin by the liver is reduced. While anti-thrombin in the environment is degraded by enzymes released from neutrophils, this results in the continuation of DIC process. It is not uncommon for shock to occur in DIC. It has been observed that shock can precipitate DIC and may contribute to its prolonged course. This, in turn, effects the macrophages of the reticuloendothelial system clearance ability, for the synthesised tissue factor, activated coagulation factors and fibrin degradation products (Figure 2).[17]

As a consequence of the rapid depletion of platelets and clotting factors associated with acute DIC, the platelet count may be below 50,000/L at admission time, which occurs in 10-15% of cases, with PT and aPTT exhibiting marked prolongation, and D-dimers demonstrating elevated levels. [18, 20] The results of intrinsic and extrinsic (PT, aPTT) and common pathways, are indicative of the concentration of factors X, V, II and fibrinogen (see Figure 1). This is the "common" pathway for both extrinsic and intrinsic pathways, resulting in the activation of thrombin and the conversion of fibrinogen to fibrin. Additionally, Prothrombin level serves as an indicator of the factor VII concentration within the extrinsic way. In this pathway, factor VII is activated by tissue factor and then proceeds through the common pathway, leading to thrombin activation and fibrin clot formation. The aPTT level serves to reflect the levels of factors VIII, IX, XI and XII present within the intrinsic pathway. The intrinsic pathway is initiated by collagen or polyphosphate activating Factor XII, which subsequently activates the common pathway and forms a fibrin clot. The prolonged prothrombin time and activated partial thromboplastin time observed in DIC are a consequence of the consumption of clotting factors. Thrombin activity is increased in acute DIC, due to three factors: increased consumption of antithrombin, increased degradation of antithrombin by neutrophil

elastase release, and reduced synthesis of Antithrombin by the liver due to microvascular thrombosis. A reduction in protein C levels is also observed as a consequence of a decline in thrombomodulin levels, which is attributable to the delivery of tumour necrosis factor α, IL-1 and IL-6 as acute phase reactants. This, in turn, results in a diminution in thrombin inactivation and an enhancement in the formation of thrombosis.[16]

Diagnosis

There is no definitive biochemical marker to diagnose DIC. Diagnosis of DIC is a clinical and laboratory diagnosis based on laboratory findings of coagulopathy and/or fibrinolysis following an underlying clinical condition (e.g. sepsis, malignancy). According to the parameters in the algorithm defined by the International Society on Thrombosis and Haemostasis, following the modifications made to the algorithm by Taylor et al, DIC is diagnosed with 93% sensitivity and 97% specificity when scored 5 or more points (Table1).[21]

The Scientific Committee of the Japanese Association for Acute Medicine has proposed another algorithm for acute DIC. The scoring system is based on the presence/absence of systemic inflammatory response syndrome, degree of thrombocytopenia, amount of elevated fibrin degradation products and whether INR is above 1.2. (Table1).[22]

Management of DIC

Treatment of the primary disease

Treatment of DIC is a topic of ongoing debate within the medical community. However, a set of treatment guidelines has been published, which provide broadly similar recommendations. The primary objective of treatment should be to address the underlying disorder. If the underlying condition is effectively managed and treated, DIC has been observed to resolve spontaneously in a significant number of cases. Most guidelines agree on this point, despite the lack of high-quality evidence on the effectiveness of treating the underlying condition. However, early intervention may be necessary to prevent complications from haemorrhage and thrombosis during the treatment of the underlying disease.[23,24]

Transfusion therapy with platelets and fresh frozen plasma

Significantly low platelet counts, coagulation factors and in particular fibrinogen levels have been shown to be associated with an increased risk of bleeding. Current guidelines recommend that patients with disseminated intravascular coagulation who have active bleeding or are at high risk of bleeding and require invasive procedures should receive platelet concentrate and fresh frozen plasma. However, there is currently a lack of high-quality evidence to support this recommendation. The decision to transfuse platelets depends on the clinical signs. Generally platelet concentrate transfusion is indiacted to the patients with active bleeding and a platelet count below 50×10^9/l or non-bleeding DIC patients with a platelet count below 20×10^9/l. A transfusion of fresh frozen plasma is typically indicated in cases of massive or DIC bleeding also. The correction of coagulation defects associated with prolonged APTT or PT (more than 1.5 times the normal value) or decreased fibrinogen level (less than 1.5 g/dl) requires the administration of large volumes of fresh frozen plasma. It is recommended that an initial dose of 15-30 ml/kg of fresh frozen plasma be administered for treatment purposes.[23,25-27]

Administration of smaller volumes of prothrombin complex concentrate may be beneficial in cases where volume overload may potentially lead to complications in patients.

In cases of massive haemorrhage in DIC due to fibrinogen deficiency, purified fibrinogen concentrates or cryoprecipitate are recommended. The majority of prothrombin complex concentrates contain vitamin K-dependent factors (II, VII, IX and X) and anticoagulants like protein S, protein C and antithrombin. Nevertheless, they are deficient in crucial coagulation factors, such as FV. Vitamin K represents a useful alternative for the correction of vitamin K-dependent clotting factors; however, its impact will not be significant until more than six hours have elapsed.[28] The administration of fibrinogen, whether as a fibrinogen concentrate or cryoprecipitate, may be of particular importance in cases where fibrinogen is deficient. The aim is to maintain fibrinogen levels above 1.5g/dl in patients with bleeding.[24] However, for women with concurrent postpartum haemorrhage, a higher level (above 2.0g/dl) is recommended.[29] Giving 30 mg fibrinogen concentrate per kg bodyweight is associated with a 1 g/dl increase in fibrinogen.[30]

Heparin as Anticoagulan Therapy

Kongstad et al. reported that heparin treatment was beneficial in DIC and especially in early DIC. [31] A well-evaluated retrospective cohort study was conducted to investigate the efficacy of heparin and LMWH in patients with coronavirus. The results showed that those who failed to receive heparin were significantly more likely to die.[32]

Table 1. Dissemine intravascular coagulation diagnosis according to International Society on Thrombosis and Haemostasis and scientific committee of the Japanese Association for Acute Medicine

Parameters	Points	*International Society on Thrombosis and Haemostasis*	*Japanese Association for Acute Medicine*
		Laboratory result	Laboratory result
Platelet count	3		<80.000
			Reduction more than ≥50% in 24hour
	2	<50000	
	1	≥50000 - <100000	≥80000 - <120000
			Reduction more than ≥30% in 24hour
D-Dimer	3	Strong increase	≥25 µg/mL
	2	Moderate increase	
	1		≥10, <25 µg/mL
PT	2	≥6 sec	
	1	≥3sec, <6 sec	INR≥1.2
Fibrinogen	1	<100	
SIRS score	1		>3
SOFA score	2		
	1		
Total Score		≥5	≥4

In a further cohort study with a lower quality evaluation, mortality rates were found to be 83% in patients treated with heparin and 86% in those not treated with heparin. This suggests that there is no significant difference between the two groups. Nevertheless, in this study, the majority of patients developed multiple organ failure with DIC, and the number of cases was relatively low.[33]

A retrospective analysis of patients with sepsis who developed DIC in 2022 revealed that the administration of unfractionated heparin at prophylactic or therapeutic doses via subcutaneous or continuous intravenous infusion was associated with a reduction in 28-day mortality and hospital mortality rates, as well as a favourable safety profile, particularly in relation to intracranial and gastrointestinal bleeding.[34] A further retrospective analysis of a comprehensive database demonstrated that the early commencement of prophylactic doses of unfractionated heparin was linked to a reduction in hospital mortality.[35] In a randomised controlled study conducted by Jaimes et al. on patients with sepsis, 28-day mortality was examined, and no significant difference was found between the heparin-treated group and the control group. Similarly, Liu et al. observed that the administration of low-molecular-weight heparin had no impact on mortality rates (31.8% to 40%).[36, 37]

The International Consensus on Thrombosis and Haemostasis does not recommend thromboprophylaxis in patients with DIC who are bleeding or have a platelet count of less than $20x10^9$/L. For patients with acute promyelocytic leukaemia, thromboprophylaxis is indicated, with a lower threshold for platelet transfusion of 20x109/L.[38]

As bleeding is the predominant feature of obstetric disseminated intravascular coagulation (DIC) patients, it is advisable to initiate treatment in those with predominant thrombotic findings.[39] Patients diagnosed with DIC and presenting with purpura fulminans, acral ischaemia, or venous thromboembolism should be initiated on a therapeutic dose of heparin. [24,28]

Conclusion

Despite recent advances in understanding the pathogenesis of DIC, the prognosis for patients remains poor. Mortality rates are increasing, especially in cases where the diagnosis is made late. The lack of a definitive laboratory biomarker increases the importance of the physician in the diagnosis of DIC. In the early period after an underlying disease, confirmation of the diagnosis of DIC using scoring systems and early initiation of anticoagulant therapy for thrombotic complications and replacement therapy for bleeding will make a positive contribution to reducing mortality.

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