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Modality For Disseminated Intravascular Coagulation And Current Treatment

Yaren Dirik[1*], Pınar Kolusarı[2]

[1]*Van Ozalp State Hospital, Department Of Internal Diseases, Van, Turkey*
[2]*Van Troining And Research Hospital, Department Of Anesthesiology And Reanimation, Van, Turkey*

ABSTRACT

Disseminated Intravascular Coagulation (DIC) is a systemic syndrome that causes thrombosis in small and medium-diameter vessels as a result of disruption of hemostatic balance by several reasons, and progresses with the consumption of thrombocyte and coagulation factors, severe hemorrhage and impaired organ perfusion as a result of activation of disseminated intravascular coagulation mechanism. DIC is always a complication that occurs together with some diseases and various secondary pathological conditions. The tissue factor which occurs as a result of tissue factor firstly activates the coagulation cascade; and overproduction of thrombin forms the basis of pathogenesis of DIC. The clinical course of DIC is generally under the influence of the underlying etiologic factor. There is not a laboratory test diagnosing DIC alone; however, the laboratory findings are indispensable for diagnosis. Treating the disease causing DIC and predominant signs of bleeding or thrombosis in clinical table, and conducting prophylaxis for preventing repetitions in chronic DIC cases are the main steps of treatment.

Key Words: Disseminated Intravascular Coagulation, Treatment, Diagnosis

Introduction

Disseminated Intravascular Coagulation (DIC) is a systemic syndrome that causes thrombosis in small and medium-diameter vessels as a result of disruption of hemostatic balance by several reasons, and progresses with the consumption of thrombocyte and coagulation factors, severe hemorrhage and impaired organ perfusion as a result of activation of disseminated intravascular coagulation mechanism. There are different definitions in literature, such as disseminated intravascular coagulation or consumption coagulopathy (1-3).

Because of the lack of primary pathology, DIC is always a complication that occurs together with some diseases and various secondary pathological conditions. It may occur as a result of many reasons such as severe infections and sepsis, cancers, traumas causing severe tissue damages, hypoxia, obstetric complications, some cardiovascular diseases, immunological diseases, and toxin-based reactions (4).

In spite of the scientific progresses, there are still many difficulties and divergences related to standard diagnostic criteria and treatment of DIC because many different diseases play a role in the pathogenesis of it and also clinical and laboratory courses of disease differ from each other (5).

The mortality and morbidity of DIC are still very high nowadays. Therefore, effective treatment gains importance.

Pathophysiology: DIC is a syndrome that presents as a response to endothelial damage caused by different reasons and occurs as a result of excessive and uncontrolled hemostasis activation (6).

The tissue factor which occurs as a result of tissue factor firstly activates the coagulation cascade; and overproduction of thrombin forms the basis of pathogenesis of DIC. Systemic fibrin accumulation caused by tissue factor-mediated thrombin formation suppresses physiological anticoagulants; and fibrinolysis is disrupted via plasminogen activator inhibitor-1 (PAI-1). The major proinflammatory cytokines which are released during DIC are interleukin-6 and TNF-a. Interleukin-6 mediates activation of coagulation, and TNF-a mediates inhibition of physiological anticoagulant pathways and fibrinolysis (1, 7, 8).

The endothelium is the most important regulator of coagulant, anticoagulant and fibrinolytic systems because it is an anticoagulant in health and is an organ which facilitates clotting when it is damaged. Tissue Factor (TF) is released as a result

***Corresponding Author:** Yaren Dirik, Ozalp State Hospital, Department of Internal Diseases, Van, Turkey
E-mail: yaren.dirik@gmail.com, Phone: 0 (506) 690 59 71
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of damaged endothelium transforming factor VII -through activating it- into factor VIIa in the extrinsic pathway. VIIa starts the coagulation system from intrinsic and main pathways together through transforming factor IX -through activating it- into factor IXa in the intrinsic pathway, and transforming factor X -through activating it- into factor Xa in the main pathway. Synchronous Tissue Factor Pathway Inhibitor (TFPI) is also released from endothelium; and therefore, the release of the tissue factor is controlled. In addition, collagen presenting under damaged endothelium transforms factor XII -through activating it- into factor XIIa via prekallikrein (PK) and High-Molecular-Weight Kininogen (HMWK) (9). This causes the activation of coagulation cascade in intrinsic pathway via leading to constant XIIa construction and then through transformation of factor XI into XIa through activation of XI.

Natural anticoagulants such as Antithrombin (AT), protein C system, Tissue Factor Pathway Inhibitor (TFPI), heparin cofactor-II, and thrombomodulin, which play important roles in limiting the production of thrombin to the damaged region, are insufficient in patients with DIC because of uncontrolled and systemic thrombin production (10). Antithrombin is an important natural anticoagulant that inhibits mainly thrombin and FXa, and also FIXa, FXIa, FXIIa and FVlIa-TF complex. Inadequate AT level increases fibrin formation.

Protein C activation in physiological hemostasis is a mechanism against excessive fibrin formation. Protein C activation occurs after binding to the thrombin-thrombomodulin complex. After thrombin binds to thrombomodulin, it loses its coagulant characteristics. After protein C activation (activated protein C-APC formation), it inhibits FVA and FVIIIa with the cofactor role of Protein S and reduces thrombin production. It is known that Protein S and Protein C levels decrease significantly in DIC cases (11, 12).

In addition to the decrease of natural anticoagulants, uncontrolled release of Plasminogen Activator Inhibitor-1 (PAI-1) from stimulated endothelium causes the inhibition of the fibrinolytic system. As a consequence of all this, widespread microthrombosis is seen in the vessel due to excessive thrombin formation (2, 13).

Because of the presence of thrombin receptors on the membrane of thrombocytes, thrombin is also a strong thrombocyte activator. Thrombocyte activation that occurs in the pathogenesis of DIC causes thrombocytopenia due to their excessive consumption (13-15). It also leads to thrombocytes dysfunction through binding fibrin degradation products (FDP) to GP IIb/IIIa receptors in thrombocytes. The fact that DIC is a clinical entity consisting of common thrombosis and bleeding diathesis may be attributed to the consumption of coagulation factors and antithrombin (16, 17).

It was previously reported that in some cases mitochondrial matrix-located mtDNA infiltrates into cytoplasm from organelle and joins into body fluids including blood, urine, saliva, cerebrospinal fluid, and joint fluid by leaking into extracellular matrix (18,19-22). The organelle DNA found in body fluids is called free mtDNA (circulating cell-free mtDNA / ccf-mtDNA).

Although the leakage mechanism of mtDNA into systemic circulatory system is not yet known, many different physiological conditions causing oscillation had been reported until today. The circulating mtDNA could be stemmed from the cells affected by tissue damage or various cells that are involved in inflammatory mechanisms. Zhang et al. reported that mtDNA is released into circulation system due to cell structure and mitochondrial injury associated to tissue damage after trauma and hemorrhagic shock (23,24).

The presence of ccf-mtDNA in the samples obtained from healthy individuals suggests that there might be a mechanism that leads to the regular passage of mtDNA to the extracellular matrix and finally to the systemic circulation in the normal physiological state (18,25).

Whether in free form or in microparticles ccf-mtDNA is a strong hazard signal recognized by the natural immune system and has an important function in adjusting the inflammatory response. It was shown that ccf-mtDNA could play a central role in the connection between systemic inflammation and mitochondrial damage (26). The molecules that participate into circulatory system by leaking from cells after tissue damage and stimulate natural immune system are called Damage Associated Molecular Patterns (DAMPs). It was known that cellular ccf-mtDNA present in systemic circulation acts as DAMP when mitochondrial quality control mechanisms fail due to cellular stress besides apoptotic and necrotic cell deaths (27,28,29).

The Clinical Course: The clinical course of DIC is generally under the influence of the underlying etiologic factor. There are two interrelated courses that are defined acutely and chronically (14, 15).

Table 1. ISTH Scoring for Overt DIC

Parameters		Score
Thrombocyte count		>100/nl= 0
		50-100/nl= 1
		<50/nl= 2
PT (INR)	(< 3 sec = 0)	<1.25 = 0
	(3 – 6 sec = 1)	1.25 – 1.67 = 1
	(> 6 sec = 2)	>1.67 = 2
D-Dimer		<2xULN = 0
		2-5xULN = 2
		>5xULN = 3
Fibrinogen		≥1g/L = 0
		<1g/L = 1
Evaluation	Make scoring as	≥5 points: Overt DIC
		<5 points: Non-overt DIC (Dynamic)

ULN: Upper Limit of Normal

Severity of the clinical course -depending on the rate of activation of coagulation- is determined by the rate of use of coagulation substrates, effectiveness of fibrinolysis in fibrine destruction, and also on the rate of regeneration of used thrombocytes and coagulation factors by bone marrow and liver. In acute DIC, there is a mechanism in which widespread coagulum formation and/or coagulation factors are used. This condition cannot be compensated by the fibrinolytic system and/or liver-bone marrow (1, 2, 13). This systemic collapse is presented by severe bleeding, widespread thrombosis and multiple organ failure. The most dramatic scene in acute DIC is bleeding. Bleeding starts primarily from frequent blood draws, nasogastric tubes or surgical incision sites. At the place where the blood is drawn or there are wounds, ecchymosis, soft palate; and petechias on skin occur. Large subcutaneous hematoma and deep tissue bleedings are also often observed. Tissue necrosis can develop in many organs; infarcts may appear in the large part of the skin, subcutaneous tissue or in the kidneys. It results in hemolysis anemia due to microangiopathy. Bleeding and fluid leakage to third spaces leads to hypovolemia and hypotension (16, 17). Functional loss occurs in major organs such as heart, lung, kidney, liver and brain due to hypoxic damage, microvascular thrombosis and bleeding. Clinically, hypoxia agitation, dyspnea, tachypnea and cyanosis are seen. In early period, neurological findings such as visual impairment, headache, confusion, inappropriate behaviors, muscle weakness, hemiplegia or coma are seen due to cerebral hypoxia, decreased cardiac output, microthrombosis in small vessels, and intracranial bleeding (30, 31).

In chronic DIC, the balance among the production of coagulation, fibrinolysis, and coagulation factors is not impaired enough to produce a severe clinical or laboratory scene as in acute DIC. Prothrombotic disorders are seen in chronic DIC usually; however, bleeding may not occur. Microvascular thrombosis, which occurs due to fibrin accumulation in the organs and which causes multiple organ failure, leads to less clinical signs (32, 33). Mild coagulation test disorders and/or thrombocytopenia are usually detected with an asymptomatic clinical course or thrombosis. The hemostatic system suffers from chronic DIC; however, it is not decompensated. It is stimulated enough to overcome endothelial anticoagulant functions in the coagulation system. It may cause venous and arterial thrombosis for patients, and it is seen as increases with fibrin degradation products (FDP) (34). Clinically, Deep Vein Thrombosis (DVT) or Mobile Superficial Thrombophlebitis (Trousseau's Syndrome) can be seen on extremities. Arterial thrombosis also causes digital ischemia, renal infarction, paralysis, and non-bacterial endocarditis (14, 16, 34).

Diagnosis: There is not a laboratory test diagnosing DIC alone, however, laboratory findings are indispensable for diagnosis.

There is absolutely thrombocytopenia and microangiopathic hemolytic anemia in acute DIC. The degree of thrombocytopenia and findings of microangiopathic hemolytic anemia should be assessed with peripheral dissemination. Decreases in lifespan of thrombocyte and increase in turn-over of thrombocyte due to microthrombosis are

Table 2. Dynamic ISTH Scoring for Non-overt DIC

		Score
Does the underlying disease make DIC?		No: 0 Yes: 2
Thrombocyte count	Day 1	increase = -1
	≥100/nl = 0	stable = 0
	<100/nl = 1	decrease = 1
PT (INR)	Day 1	decrease = -1
	≤1.25 = 0	stable = 0
	>1.25 = 1	increase = 1
D-Dimer	Day 1	decrease = -1
	<2xULN = 0	stable = 0
	≥2xULN = 1	increase = 1
Antithrombin	≥70% = -1	
	<70% = 1	
Protein C	≥70% = -1	
	<70% = 1	
Evaluation		≥5 points: Overt DIC <5 points: No DIC

ULN: Upper Limit of Normal

reflected as giant microthrombosis to the peripheral extension. In the peripheral extension, schistocytes are seen in approximately 50% of patients. Schistocytes are the markers of microangiopathic hemolytic anemia; however, no relation has been determined between the degree of schistocytes and disease prognosis (35).

In the diagnosis of DIC; both the increase in thrombin production and the overactivation of the fibrinolytic system must be demonstrated. It is seen through a decrease in fibrinogen level, an increase in fibrin degradation products and in D-Dimer level. The amount of the change in these parameters is related to the end-organ damage and mortality, and since the degeneration in these parameters does not always occur simultaneously, it is necessary to repeat it intermittently to confirm the diagnosis (1, 13-15). The increase in D-Dimer level is not specific to DIC; however, it is the most common laboratory finding. FDP levels in serum increase at a rate of 80-100% in patients with DIC. However, since it is quickly removed from circulation, the absence of FDP does not exclude the DIC. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (PT, aPTT) extend due to decrease in coagulation factor. Fibrinogen is generally low in acute decompensated DIC; however, it can be detected as normal in patients with a high pre-fibrinogen level since it also has an acute phase reactant (14). Very low levels of natural anticoagulants such as AT, protein C and protein S show poor prognosis (12, 36). Soluble fibrin monomer test is an important test with very high sensitivity and specificity in diagnosing DIC (37).

In chronic DIC, laboratory findings are quite changeable. PT and aPTT are usually in normal level. Mild thrombocytopenia is observed. Fibrinogen level is usually normal; however, it may also increase slightly. Diagnosis in these patients is made through demonstrating microangiopathic hemolytic anemia (schistocytes) in peripheral extension, and detecting increased D-Dimer and fibrin degradation products. Synthesis site of Factor VIII is the vascular endothelium rather than liver; therefore, the finding of low level Factor VIII is in support of DIC (14, 34).

Several scoring systems are developed for diagnosis of DIC. Diagnostic criteria for DIC were published by the International Society of Thrombosis and Hemostasis (ISTH)/Scientific and Standardization Committee (SSC) in 2001 (Table 1-2) (38). DIC is a dynamic process and scoring should be repeated during the course of the disease (14).

Treatment: Treatment is based on the treatment of the disease causing the DIC. Then, support and replacement treatments, and the coagulation mechanisms are controlled. Treatment should be individualized according to the cause and severity of DIC. Treating the disease causing DIC and

predominant signs of bleeding or thrombosis in clinical table, and conducting prophylaxis for preventing repetitions in chronic DIC cases are the main steps of treatment (14).

Treatment Options for DIC

- Replacement Treatment [Fresh Frozen Plasma (FFP), Thrombocyte Suspensions (TS)]
- Anticoagulants [Unfractionated heparin or Low-Molecular-Weight Heparin (LMWH), Danaparoid sodium, Recombinant hirudin, Recombinant tissue factor pathway inhibitor (rTFPI), Recombinant nematode anticoagulant protein c2 (rNAPc2)]
- Regulation of the Natural Anticoagulant System [Antithrombin (AT), Recombinant human activated protein C (rhAPC)]
- Other drugs [Recombinant activated factor VII (rFVIIa) (NovoSeven), Antifibrinolytic agents, Recombinant interleukin-10 (rIL-10), Anti-selectin antibodies, Monoclonal antibodies against TNF and CD14]

If there is bleeding, transfusion should be used absolutely. When the thrombocyte count is below 50.000/ml, a random thrombocyte (5-10 units) or apheresis thrombocyte suspension should be given. When fibrinogen level is below 100 mg/dL, 10 units of cryoprecipitate or fibrinogen solutions should be given. If hematocrit is lower than 30%, erythrocyte suspension is given; and also, when the range is above 2.0 and aPTT is high, 15 ml/kg fresh-frozen plasma is given. Since TDP transfusion (15 ml/kg, each 4-6 hours) covers large volume, factor concentrates can be used instead of it. However, some concentrates may not include coagulation factors. Also, these concentrates may include activated coagulation factors in trace quantity and it may greatly increase coagulation. The efficacy of treatment can be assessed by PT and aPTT. If there is vitamin K deficiency in patient, vitamin K should also be given (1, 14, 39, 40).

Heparin can be used in acute DIC especially when thromboembolism is predominant (such as purpura fulminans). In chronic DIC, if the case progresses with recurrent thrombosis (such as solid tumors, hemangioma, dead fetus syndrome), heparin is used. Low molecular weight heparin (danaparoid sodium) is also used for the same cases (41). Heparin is used to block thrombin activation due to excessive thrombin generation in DIC. However, the main problems of heparin treatment are the need of sufficient AT with which heparin can work (low AT is problem in DIC), the potential for thrombocytopenia occurring due to heparin, and the release of endogenous inhibitors (such as platelet factor 4, lactoferrin) against heparin and decreasing the effect of it. Heparin dose should be 5-10 units/kg /hour (500-750 units/hour) and loading dose should never be used (42). aPTT is not safe due to existing coagulopathy (43). The patient must have sufficient antithrombin level (80-100%) for the heparin to be effective.

Thrombocytopenia does not occur with hirudin, which blocks the formation of thrombin; and tissue factor release is reduced on the surface of the endothelium. Recombinant hirudin (Lepirudin) given after endotoxin-induced activation of the coagulation reduces the thrombin formation and tissue factor release on the monocyte surface (14). It was showed that the use of direct thrombin inhibitor ximelagatran (melagatran) in combination with dexamethasone prevented DIC (44).

The most important anticoagulant that should be used when considering pathogenesis in DIC should be the agents that inhibit tissue factor activation. Recombinant NAPc2 (Nematode Anticoagulant Protein c2) which inhibits triplets of the Recombinant Tissue Factor Pathway Inhibitor (rTFPI), tissue factor/factor VIIa and factor Xa can be mentioned among these potential agents (45). It is shown that BCX-3607, a potent inhibitor of tissue factor fVIIa, reduces thrombus formation and IL-6 levels (16). Although Phase II studies with r-TFPI in patients with sepsis are highly promising in treatment, any survival advantage with this agent in phase III trials have not been shown (46). It was also shown that NAPc2 (Nematode Anticoagulant Protein c2), which specifically suppresses fusion of TF/fVIIa with fXA, inhibits coagulation activation in primate sepsis models (47).

In DIC, the level of natural anticoagulants (Antithrombin, Protein C and S) is low due to overuse. Antithrombin (AT) is a natural inhibitor of thrombin circulation. The AT is also a protein with anti-inflammatory properties. In a multi-centered, randomized, double-blinded, placebo-controlled study, it was shown that, treatment with AT concentration in patients with sepsis and post-operative complications became useful in patients in need of respiratory and hemodynamic support over 30 days of lifespan (48). In contrast, another double-blinded, placebo-controlled, multi-centered study, it was shown that high-dose AT did not prolong the 28-day survival of patients with severe sepsis, and it increased bleeding in the patients who were given AT and heparin together (49).

Since Activated Protein C (APC) is anticoagulant and anti-inflammatory, Recombinant Human Activated Protein C (rhAPC) can be used in secondary severe DIC with sepsis (50). In a Phase III study of 1690 patients with sepsis with recombinant human activated protein C (Drotrecogin alpha-activated), it was shown that mortality was reduced by 19.4% in patients receiving drotrecogin alpha activated at a dose of 24 μg/kg/hour for 96 hours (51). However, the rate of serious bleeding was also higher in these patients. D-Dimer and IL-6 levels were also found to be low in patients receiving drotrecogin alpha activated. In another study, decrease in a 28-day mortality rate and a faster recovery of organ dysfunctions were shown in patients with severe sepsis and given Recombinant Activated Protein C (rAPC) (52).

On the contrary, in another prospective study, no significant difference was found between the placebo group and the patient group (53). If rhAPC is used in the treatment, it should be considered that thrombocyte count should be more than 50.000, INR should be below 2.0 and aPTT should be less than 1.8 times the normal range, and -when necessary- thrombocyte suspensions and/or fresh frozen plasma should be used to provide these levels (54).

Anti-fibrinolytics such as epsilon-aminocaproic acid or tranexamic acid have rarely been used in DIC cases; however, they should not be used if possible. However, heparin must be given together if it will be used because anti-fibrinolytic agents inhibit the fibrinolytic system and cause tissue perfusion deterioration and thrombosis (55). DIC may sometimes be seen together with primary fibrinolysis in cases such as Acute Promyelocytic Leukemia (APL), giant hemangioma, heat stroke, amniotic fluid embolism, some liver diseases and metastatic prostate cancers. When such patients cannot receive any responses to treatments, they may benefit from anti-fibrinolytic treatment (56).

A case with severe intra-abdominal bleeding that did not respond to other treatments was also controlled by treatment with Recombinant Activated Factor VII (rfVIIIa) (57).

Monoclonal antibodies against CD14 acting as receptors for anti-inflammatory cytokines such as IL-10, anti-TNF bacterial endotoxins have also been used in experimental studies (41).

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