



Received for publication, November, 23, 2017
Accepted, December, 13, 2017

Original paper

New biomolecules for the treatment of Disseminated Intravascular Coagulation

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Abstract

Disseminated intravascular coagulation (DIC) is a clotting disorder characterized by a hypercoagulation state that can lead to multiple organ failure as a final complication. There are two forms of DIC, acute and chronic. It is usually determined by the exposure of the tissue factor and the activation of the extrinsic pathway of coagulation cascade. DIC often appears as a complication of sepsis, trauma, obstetrical emergencies and neoplastic conditions. Acute DIC includes symptoms such as bleeding, hepatic, kidney or respiratory failure, while chronic DIC associates thrombotic complications. For paraclinical diagnosis, the International Society on Thrombosis and Haemostasis uses a lab score that includes platelet count, fibrinogen, PT, D Dimers values. This score is not 100% specific so differential diagnosis should be made. The therapeutic approach requires life functions supervision, control of hemorrhage and thrombosis with new supportive strategies, antibiotherapy for septic patients and surgical intervention if needed. New strategies aimed at the inhibition of coagulation activation using biomolecules are available. Management of thrombotic, hemorrhagic or septic patients requires a multidisciplinary team, involving ICU doctors, hematological specialists, biomedical researchers, surgeons and the availability of a Blood Transfusion Centre.

Keywords

Disseminated intravascular coagulation, new biomolecules.

To cite this article: NITIPIR C, ANA NEAGU M, IACIU C, BARBU MA, POPESCU BC, ORLOV C, POPA AM, CONSTANTINESCU R, PIETROSANU C, PITURU S, HAINAROSIE R, STOIAN AMP, STANCIU AE. New biomolecules for the treatment of *Disseminated Intravascular Coagulation*. 2019; 24(4): 580-585. DOI: 10.25083/rbl/24.4/580.585

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Introduction

Disseminated intravascular coagulation (DIC, also called consumption coagulopathy and defibrination syndrome) is a clotting disorder resulting from the excessive pathological production of thrombin and fibrin in the blood and giving rise to a hypercoagulation state characterized by the formation of small and large thrombi, tissue lesions and organ failure. The thrombin impact on the coagulation cascade (Figures 1 and 2) entails the consumption of clotting factors (platelets, fibrinogen, factor V, factor VIII, C protein, antithrombin) and secondary fibrinolysis that ultimately leads to bleeding. The DIC is essentially a thrombohemorrhagic syndrome involving multiple organ failure among its final complications [1, 2, 3].

Materials and Methods

The present paper represents a general review of disseminated intravascular coagulation, from an oncological perspective. Information from both reference medical textbooks and latest clinical trials on this matter was synthesized to accurately present this perspective. Depending on the time of onset and acuteness, as well as the patient's associated comorbidities, there are two forms of DIC: the acute form (evolving in hours, days) mainly causing bleeding (from bruises associated to parenteral administration to severe gastrointestinal bleeding) and the

chronic and subclinical form of the disease (evolving in weeks, months) associated predominantly with metabolic and thrombotic symptoms (profound venous thrombosis and pulmonary embolism). Neoplastic diseases and large aortic aneurysms are the most common causes of chronic DIC [3, 4]. The acute form is considered to be two-staged: a first hypercoagulable stage and a second hypocoagulable stage, i.e. the consumption coagulopathy arising from the excessive initial use of clotting factors and the human body's inability to produce the required factors [2]. A mild intravascular haemolysis with schistocytes identified on the smear and the deterioration of red blood cells by fibrin polymers may occur. The internal bleeding and the microvascular thrombosis cause hemorrhagic necrosis and organ failure. One percent of in-patients [5] and 30-50% of patients with sepsis are believed to suffer from DIC [6].

Results and Discussion

DIC is usually determined by the exposure and release of the tissue factor, and the activation of the extrinsic pathway of coagulation cascade. The possible causes of DIC may include sepsis (polysaccharides of Gram-negative bacteria, Gram-positive peptidoglycan), trauma – especially of the central nervous system, obstetrical emergencies (therapeutic abortion, placental abruption, dead foetus syndrome, amniotic fluid embolism, pre-eclampsia), neoplastic conditions (mucinous pancreatic and prostate adenocarcinoma, acute promyelocytic leukemia) and shock of any nature that entails an exposure to the tissue factor.

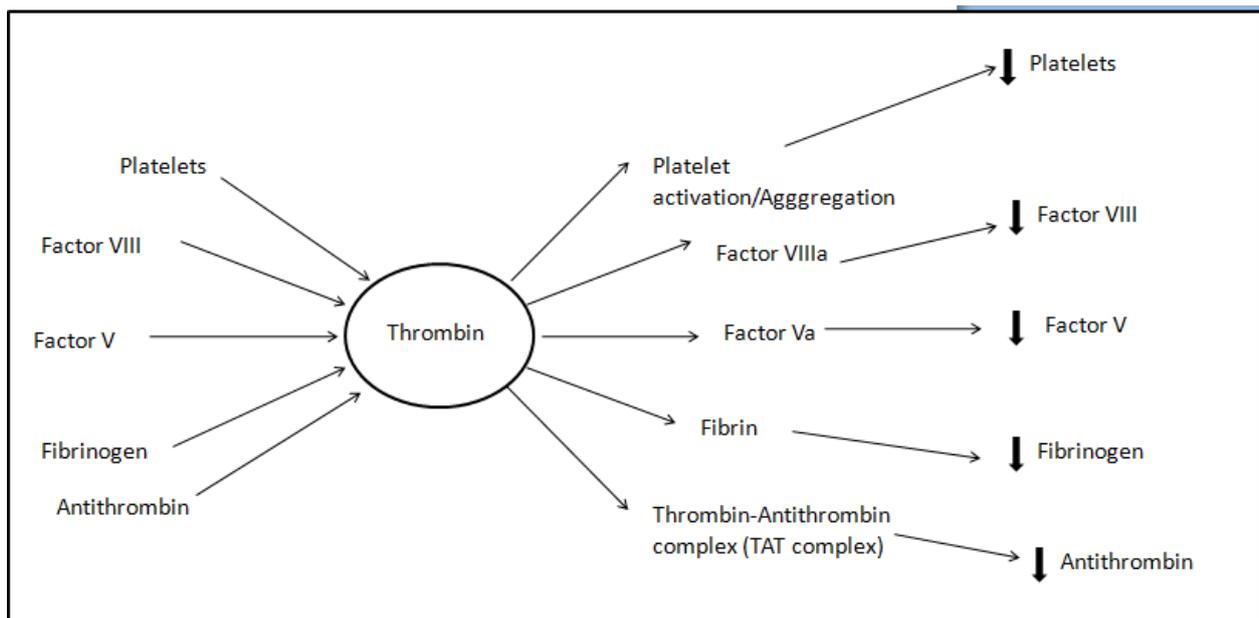


Figure 1. Thrombin Impact on the Coagulation Cascade [2].

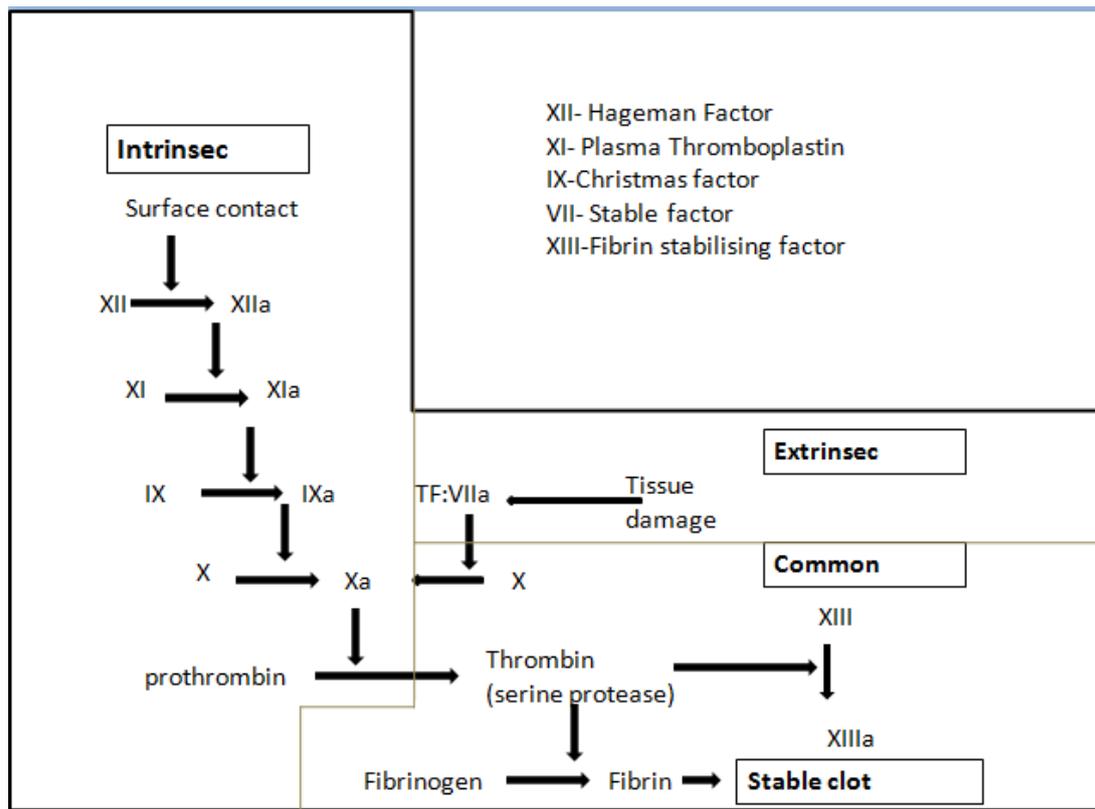


Figure 2. Coagulation Cascade [2].

DIC can represent a paraneoplastic syndrome associated with different types of malignancies, especially epithelial tumor, leukemia and lymphoma. The majority of head and neck malignancies are of epithelial origin and patients with pharyngeal (especially oropharyngeal tumors – tonsils, tongue) and laryngeal carcinomas can present DIC. In these patients DIC can also appear during surgery or after surgery. The rapid diagnosis of DIC is essential for a favorable prognostic of the patient. On the other hand early detection of malignancies is important for lowering the risk of DIC during or after surgery. One key element for early diagnostic of pharyngeal and laryngeal malignancies is thorough endoscopic examination (with white light and NBI filters) associated with in vivo staining techniques using toluidine blue, methylene blue and Lugol iodine. Assessment of the tumor cells with ELISA assay and flow cytometry can offer information during therapeutic process and follow up period of patients with head and neck malignancies.

The uncommon causes of DIC include: prostate surgery, venomous snake bites, burns, frostbites or the Kasabach-Meritt syndrome, acute hemolytic transfusion reaction, acute liver failure, pancreatitis, thermal shock [1,7]. The tissue factor exposure to the blood stream causes

the uncontrolled generation of thrombin with two major consequences: the excessive consumption of clotting factors and platelets and the occurrence of fibrin deposits in the microcirculation. The ultimate effect leads to red blood cell-damaging, tissue damage with multiple organ failure and secondary fibrinolysis. The ultimate result of all these mechanisms is diffuse bleeding [8].

Symptoms. Complications

DIC signs and symptoms vary according to its form. Acute DIC includes symptoms such as bleeding, renal, hepatic and respiratory failure and shock, while clinical manifestations associated with its chronic state are not so blatant and commonly include thrombotic complications [3].

The DIC complications include acute kidney failure, liver failure, respiratory failure, altered mental status, thrombosis and life-threatening bleeding, cardiac tamponade, hemothorax, intracerebral hemorrhage, upper and lower limb gangrene, shock and death [9]. DIC patients may show a state of confusion, lack of orientation, fever, respiratory distress and cutaneous and mucous membrane lesions (purpura, petechia, hemorrhagic bullae, acrocyanosis, thrombosis, purpura fulminans, localized gangrene) [1].

Paraclinical diagnosis

DIC is paraclinically characterized by a decrease in platelet count (thrombocytopenia) and the extension of clotting time (Prothrombin Time – PT), higher serum concentrations of fibrin degradation products and lower concentrations of fibrinogen plasma [7, 9].

The International Society on Thrombosis and Haemostasis suggests that a lab-score for DIC diagnosis involving the following tests should be established:

1. The platelet count or the fast drop in platelet count <50000 = 2, < 100000 = 1 or >100000 = 0
2. Fibrinogen <1 g/l = 1 or >1 g/l = 0
3. PT >6 seconds = 2, <6 seconds, but >3 seconds = 1 or <3 seconds = 0
4. D-dimers – significant increase = 2, moderate increase = 1 or no increase = 0 [2]

DIC diagnosis is possible if the patient scores ≥ 5 , but only if the patient suffers from a primary disease that may determine the onset of DIC. If the score is less than 5, laboratory tests will be repeated. Other causes for thrombocytopenia or protein synthesis deficiency may lead to a change in paraclinical test results. D-dimers are sensitive yet non-specific. Increased D-dimer values are found in inflammation, ascitis, pleuritis, post-operative status, soft tissue bleeding [1].

The presence of fibrin soluble monomers is indicative of coagulation cascade activation of any cause. Therefore, fibrin soluble monomer detection is sensitive, but non-specific. Fibrin degradation products (FDPs) or fibrin split products (FSPs) occur in larger numbers in the secondary fibrinolysis. The D-dimer level indicates the presence of antigen on the split reticulated fibrin rather than of an antigen for FSP. The prothrombin fragment F1+2 released during the prothrombin-thrombin conversion is significantly higher in DIC patients [2].

It is worth mentioning that laboratory test results during the DIC thrombotic stage may be within normal values and that paraclinical diagnosis may become easier to reach when the patient enters the hypocoagulable state and bleeding occurs [2].

Since DIC diagnosis is difficult, especially in the initial hypercoagulable status, a differential diagnosis with conditions associating bleeding and hypercoagulability, anemia or thrombocytopenia is mandatory. Most often differential diagnosis implies liver failure of any cause. Other common pathologies that resemble DIC are heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura [3, 8].

Therapeutic Approach

There is no medical protocol available for DIC yet. The major principle in the management of DIC is treatment of the underlying cause in order to eliminate the stimulus

for ongoing coagulation and thrombosis [2, 3]. The first therapeutic approach requires supervision of life functions, control of both hemorrhage and thrombosis, administration of blood-stopping drugs and correction of hypovolemia, if needed. Antibiotic therapy is mandatory in sepsis associated DIC, for example. Oncological treatment is urgent if the suspected cause is an oncological one. The surgical approach will be considered in a number of circumstances only, like obstetrical causes or trauma [9].

Acute DIC is a life-threatening condition because it can lead to rapid organ failure [6]. The patients' prognostic is established by the severity of the coagulopathy and of the primary disease. If the triggering condition is self-limited or treated, DIC will remit [9].

Management of Thrombotic DIC

In chronic DIC, low dose heparin administration may be a solution in clear-cut thromboembolism and events triggered by fibrin deposits (purpura fulminans, peripheral ischemia) One heparin dose of 4-5U/kg in continuous intravenous infusion demonstrates no higher risk of bleeding when compared to 80-U/kg without bolus in DIC. Heparin is a valid option in slow-evolving DIC. Even some serious conditions like dead fetus syndrome with associated DIC can be treated with heparin to delay uterine expulsion and control extensive thrombosis [1, 6, 7]. In this case, heparin is given at low doses of 500-750 U/h, without bolus. Regular PTT follow-up is mandatory. Heparin administration must be withheld if bleeding occurs [2].

Patients with homozygous protein C deficiency or acquired protein C deficiency (due to meningococemia) may develop purpura fulminans. Patients with purpura fulminans, including adults, appear to benefit from the administration of protein C concentrate [10]. In one series of 12 patients with purpura fulminans treated this way, no deaths were reported despite a predicted mortality rate of 60 to 80 percent [10]. Intravenous 100 IU/kg bolus will be administered initially, followed by 50 IU/kg every six hours until D-dimer values normalize, or show decreasing trend [11]. Administration of antithrombin concentrates is still under debate [1, 2].

Management of Hemorrhagic DIC

Deficiency of platelets and clotting factors increases the risk of hemorrhagic DIC. In the presence of bleeding, or potential need to undergo surgery, the administration of platelet concentrate, clotting factors (1-2 U of fresh frozen plasma) and fibrinogen (8-10 U of cryoprecipitate if the fibrinogen <1 g/l) may be considered. Administration 3 g fibrinogen concentrate in one dose may rise the plasma fibrinogen level by 1 g/l. Worsening of pre-existent congestive heart failure after the administration of fresh frozen plasma must be considered [2].

Thrombocytopenia is most common in patients suffering from DIC. Although the benefit of correcting thrombocytopenia in non-bleeding patients is controversial, the administration of platelet concentrate at levels of less than 10,000 platelets/microL is recommended [3, 12]. Patients with active bleeding or those who might experience active bleeding after surgery or invasive procedures need to have their thrombocytopenia corrected to more than 50,000/microL. Such correction is achieved with one or two blood platelet units per 10 kg or one platelet unit per day. This can be changed according to the extent of surgery [3].

Patients suffering from hemorrhagic DIC and biologically showing extended clotting times may receive fresh frozen plasma. If fresh frozen plasma is not available, the administration of prothrombic complex concentrate to correct the deficiency of clotting factors may be attempted. The differential diagnosis of severe DIC, acute DIC and massive hepatic necrosis relies on the factor VIII concentration level. Its' levels are higher in hepatic necrosis and lower in acute DIC [1,7, 13]. Administration of platelet concentrate to patients should be taken into consideration in patients with platelet levels less than $20 \times 10^9/L$ if bleeding is absent and between $20 \times 10^9/L$ and $50 \times 10^9/L$ in case of hemorrhage.

To correct the deficiency of clotting factors, cryoprecipitate (containing higher concentrations of fibrinogen) and fresh frozen plasma (FFP) are best options. Immediately after this, DIC may actually worsen due to certain triggering factors. Factor V is also not retrieved. Patients with $INR > 2.0$, $aPTT > 2XN$ and $fibrinogen < 100mg/dL$ may recurrently receive FFP to correct the consumption of clotting factors [14]. Initial doses start at 15 mg/kg [15].

The systematic supervision of clotting times and fibrinogen shall be considered. If required, the K vitamin deficiency shall be corrected.

Antifibrinolytic agents such as ϵ -aminocaproic acid or the tranexamic acid may be considered in hemorrhagic DIC patients, but always in association with heparin to mitigate the prothrombic effect. No antifibrinolytics shall be administered to patients suffering from asymptomatic DIC and organ failure. The immediate treatment with antifibrinolytics has to be maintained until PAI-1 levels rise [15, 16]. The administration of antifibrinolytics to hemorrhagic DIC patients whose clinical presentation is dominated by fibrinolysis (prostate cancer, acute promyelocytic leukemia) is described in the literature [2, 12].

Both sepsis and DIC are characterized by the inflammatory syndrome. A lower inflammatory response adversely affects coagulation activation and fibrinolysis. Activated C protein is important for coagulation adjustment

and factor VIIIa deactivation. Factor Va also plays a part in the activation of protease-activated receptor 1 (PAR-1) that inhibits inflammation and apoptosis [14]. The PROWESS-SHOCK clinical trial failed to demonstrate that sepsis-associated DIC may benefit from treatment with Drotrecogin Alfa (Activated C-Protein). The drug was withdrawn in 2015. Randomized clinical trials were unsuccessful at proving that the administration of anti-thrombin concentrate or recombinant PCA (Drotrecogin Alfa) reduces DIC mortality [7]. A phase III clinical trial points out to the fact that the administration of tissue factor inhibitor brought no improvement to death tolls although tests conducted on animals looked promising [17].

Other Therapeutic Options

Recombined thrombomodulin may be used to treat DIC in patients with severe sepsis and hematopoietic malignancies. One thrombomodulin dose of 0.3-30 U/mL is sufficient for thrombin inactivation. The resulting complex allows conversion of C-protein to PCA. One meta-analysis of patients suffering from DIC caused by severe infection found that the usage of recombined thrombomodulin is not associated with lower mortality rates [2, 18].

As for acute DIC patients with active bleeding, the administration of recombinant factor VIIa may be a solution, but only after a risk-benefit analysis with careful consideration of its' procoagulant effect [2].

Synthetic protease inhibitors such as Gabexatemesilate® or Nafamostat® antagonize the effects of the kinin-kalikrein system, the complement system, fibrinolysis and coagulation. Gabexatemesilate® and Nafamostat® do not significantly reduce the DIC-induced mortality rate. They may be used to treat asymptomatic and hemorrhagic DIC patients given their anticoagulant and antifibrinolytic effect [5]. The administration of Hirudin to DIC patients is still under consideration [2].

Conclusion

The treatment of Disseminated Intravascular Coagulation is still subject to controversy. DIC management requires a close interdisciplinary approach involving specialties such as ICU, Haematology, Surgery and the availability of a Blood Transfusion Centre [9]. The identification of the cause and its appropriate treatment is the first step to success. Supportive strategies using new biomolecules involving inhibition of tissue factor-mediated activation of coagulation or restoration of physiological anticoagulant pathways look promising. The prognostic of patients depends on both the rapid adoption of life support measures and their comorbidities.

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