Treatment of Disseminated Intravascular Coagulation

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Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic activation of blood coagulation, generation of thrombin, and leading to disturbance of the microvasculature. In this article, definition and diagnostic criteria of DIC depend on the International Society of Thrombosis and Haemostasis (ISTH). There is no gold standard for diagnosis of DIC, only low quality evidence is used in general practice. Many diagnostic tests and repeated measurement are required. For the treatment of DIC, there is no good quality evidence. The most important treatment for DIC is the specific treatment of the conditions associated DIC. Platelets and/or plasma transfusion may be also necessary if indicated. Nevertheless, there is no gold standard for diagnosis and treatment of DIC, we use only low quality evidence in general practice.

Keywords: *Disseminated intravascular coagulation, Blood coagulation, Coagulation factors, Thrombosis*

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Disseminated intravascular coagulation (DIC) is a common problem in hospitalized patients. Conditions associated with DIC include: sepsis or severe infection (any micro-organisms), organ destruction (e.g. pancreatitis) malignancy including solid tumours and haematologic malignancy (e.g. leukaemia, myeloproliferative neoplasm), trauma (e.g. polytrauma, neurotrauma, fat embolism), pregnancy related (including amniotic fluid embolism, abruptio placentae, pre-eclampsia), vascular abnormalities (e.g. Kasabach-Merrit syndrome, large vascular aneurysms), severe hepatic failure, severe toxic or immunologic reactions (e.g. snake bites, recreational drugs, transfusion reactions, transplant rejection)[1-3]. In Thailand, a study of Mahanupap et al, demonstrated that DIC is associated with infection and cancer[4].

DIC is a syndrome characterized by a systemic activation of blood coagulation, leading to intravascular thrombin and fibrin clot that may cause of disturbances of the microvasculature and generates organ dysfunction and bleeding. In conclusion, the pathogenesis of DIC occurs from an imbalance between normal procoagulant, and anticoagulant pathways[5-7].

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Clinical presentation of patients who diagnosed with DIC varies; they may present with abnormal bleeding and/or thrombosis in small to medium sized vessels that can cause ischaemia and skin gangrene.

The subtypes of DIC are related to the underlying diseases; a data from Wada et al[8] include as asymptomatic type, organ failure type, bleeding type, and massive bleeding type. The abnormal haemostasis in DIC patients depends on two vectors: hypercoagulation and hyperfibrinolysis. The two vectors are not very strong in an asymptomatic type or pre-DIC type of DIC. Thus, the DIC patients have no clinical bleeding or thrombosis, only abnormal coagulogram. But if the hypercoagulation pathway predominates; the patient will develop microthrombi and thrombosis; it is called an organ failure or thrombotic type of DIC. Most organ failure type patients occur in DIC associated infection. In a bleeding type or hyperfibrinolytic type of DIC; both hypercoagulation and hyperfibrinolysis pathways are strong. It has been found in leukaemia patients. But if both vectors are very strong, as is found in major bleeding after major surgery or obstetric patients, it develops consumption. So it is called massive bleeding or consumptive type of DIC.

The Diagnosis and treatment of DIC should consider the type of DIC. The concepts of diagnosis of DIC in this review are based on ISTH Sub-Committee of the Scientific and Standardization Committee (SSC).

Multiple guidelines for treatment of DIC such as the British Committee for Standards in Haematology (BCSH)[3], Japanese Society of Thrombosis and Haemostasis (JSTH)[9], and the subcommittee for DIC of the Scientific and Standardization Committee (SCC)/ International Society of Thrombosis and Haemostasis (ISTH)[10], Italian Society for Thrombosis and Haemostasis (SISET)[11]. Nevertheless, the DIC is difficult to diagnose and treat. In Thailand, there is lack of good quality evidence to treatment and no clinical practice guideline of DIC.

Diagnosis of DIC

Laboratory tests

Laboratory findings include: thrombocytopenia, fragmentation haemolytic anaemia on peripheral blood smear, increasing of fibrin degradation product (FDP), elevated D-dimer, prolongation of the prothrombin time (PT), and activated partial thromboplastin time (aPTT), decreasing of fibrinogen concentration, and protein C concentration[3].

Thrombocytopenia, platelets less than $50x10^9$/L, has been found in approximately 50% of patients[12]. The degree of thrombocytopenia correlates with thrombin generation. Therefore, a single evaluation determination of the platelet count as normal level of platelet count ($150\text{-}400x10^9$/L) has been shown to provide no benefit[3].

DIC can enhance thrombin formation, increase fibrinolytic activity and fibrin degradation products, and increase D-dimer. However, FDPs are metabolized by the liver and secreted by the kidneys. Thus, in patients with abnormal liver or kidney functions the FDP level will rise[13].

Most of the DIC patients have prolongation of PT and aPTT. The PT is prolonged in 50-75% of DIC patients. The aPTT is prolonged in 25-50% of the cases[14,15]. Approximately 50% of patients who were diagnosed with DIC demonstrate normal level or even shortened of PT and aPTT, they may be occur from circulating activated factors such as thrombin or accelerating the formation of thrombin[16]. The normal level of PT and aPTT do not exclude stimulation of coagulation system[17]. Thus, repeated monitoring of PT and aPTT is recommended. The INR is usually used in monitoring of oral anticoagulant. In patients with suspected DIC, the thrombin time (TT) also may be normal or increased[3].

The measurement of fibrinogen levels can help to diagnose DIC. Although normal level of fibrinogen is found in 57% of patients, DIC cannot be excluded because fibrinogen is an acute phase protein that represents an inflammatory process[12]. The sensitivity of low fibrinogen used to diagnose DIC is 28%[18]. Therefore, repeated monitoring of fibrinogen level is the most important laboratory blood test.

The peripheral blood smear is used to identify the fragmented red blood cells, unlikely greater than 10% of all red blood cells[3]. In some cases of chronic DIC patients, they have normal coagulation screening, only elevated of D-dimer are found. However, the presence of fragmented red blood cells on a blood smear can help to confirm the diagnosis[12].

The natural anticoagulants such as antithrombin (AT), protein C, and ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13) activity in DIC patients are reduced[7]. In contrast, elevated soluble thrombomodulin (TM), elevated PAI-I, and elevated von Willebrand factor propeptide levels are often observed in DIC cases with poor prognosis. Nevertheless, the laboratory measurement could not be analysed in general hospital[19-21].

Scoring system

DIC syndrome is dynamic. The physicians need to follow-up clinical and laboratory findings. The diagnosis of DIC should be correlated with clinical and laboratory information. The ISTH Sub-Committee of the Scientific and Standardization Committee (SSC) on DIC has recommended the use of a scoring system for DIC (Table 1)[5]. The DIC scores should be calculated in patients who present with the underlying disorders associated with DIC. The score also correlates with key clinical outcomes of the patients[3]. The patients will be diagnosed with overt DIC If DIC score $\geq$5 or non-overt DIC if DIC score <5. The sensitivity and specificity of the score is 91% and 97%[22]. Several studies using the ISTH algorithm have demonstrated that overt DIC has poor outcomes and mortality[23-25]. DIC in Thailand has demonstrated a high mortality rate and poor outcome in overt DIC[4].

In conclusion, the diagnosis and treatment of DIC should be based on clinical presentation and laboratory test. In general hospital, a serum D-dimer and a serum fibrinogen level should not be evaluated. So if the patients have rapidly thrombocytopenia and abnormal coagulogram, the only diagnosis is DIC.

Treatment of DIC

Treatment of the underlying disease

Treatment of the underlying disorder is the

Table 1. ISTH diagnostic scoring system for DIC[10]

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC ?
- If yes: proceed
- If no: do not use this algorithm
Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)
Score the test results
- Platelet count (>100 x 10^9/l = 0, <100 x 10^9/l = 1, <50 x 10^9/l = 2)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 sec = 0, >3 sec but <6 sec = 1, >6 sec = 2)
- Fibrinogen level (>1 g/l = 0, <1 g/l = 1)
Calculate the score:
- ≥5 compatible with overt DIC: repeat score daily
- <5 suggestive for non-over DIC: repeat next 1-2 day

first priority in cases with bleeding, organ failure, and asymptomatic types of DIC[7]. For example, the administration of antibiotics or surgical drainage in DIC related sepsis, administration of all-trans retinoic acid (ATRA) in DIC related acute promyelocytic leukaemia. The four guidelines have consensus to treatment of underlying disease, but no high quality of evidence[3,9-11]. In contrast, DIC may be spontaneously resolved even without treatment of the underlying disease. There are no meta-analysis or randomized controlled trial studies (RCTs) to evaluate.

Blood transfusion

Blood transfusion is required in patients with bleeding and massive bleeding type[3,7,9-11].

1) Platelet concentration is recommended in patient with active bleeding, and a platelet count less than 50x10^9/l. In non-bleeding patients who develop DIC after undergoing chemotherapy the lower threshold of platelet (10-20x10^9/l) can be used. Prophylactic platelet transfusion is not recommended. There are no RCT about dose level of platelet count in patients with DIC associated with infection, trauma, blood transfusion, only in patients who develop DIC after chemotherapy[3,7].

2) Fresh frozen plasma (FFP) should be considered in prolonged PT, and aPTT patients who develop massive bleeding or a bleeding type of DIC. Laboratory data alone is not enough to give transfusion of FFP, therefore it is important to combine clinical bleeding with laboratory findings to make a decision for the appropriate treatment. The initial dose of FFP is 15 ml/kg. The goal of PT and aPTT level is less than 1.5 times the normal value. Monitoring fluid overload should be considered. Factor concentrates, such as prothrombin complex concentrate, should be considered in patients with bleeding and fluid overload[3,7,9-11].

3) Fibrinogen and cryoprecipitate are recommended in DIC with severe hypofibrinogenemia (fibrinogen level less than 1 g/l)[3,10-11].

Anticoagulants

Heparin

Therapeutic dose unfractionated heparin (UFH) should be considered in DIC with thrombotic complications such as venous or arterial thrombosis, severe purpura fulminant, and vascular skin infarction. In some cases with co-existing high risk bleeding may be beneficial to use continuous infusion UFH due to its short half-life and reversibility. Each body weight must be used to adjust dose of UFH is 10 mg/kg/h, and there is no need to maintain a prolonged the aPTT ratio to 1.5-2.5 times the control. But the monitoring aPTT is needed in high risk of bleeding patients[3,9,10].

A recent a systemic review and a meta-analysis study to evaluate the efficacy and safety of heparin both UFH or LMWH, including patients with sepsis, severe sepsis, septic shock or DIC associated infection, evaluate of 6 from 9 RCTs, a comparison between heparin and placebo has shown a decrease mortality in the heparin group (risk ratio to death 0.88 (95% CI, 0.77-1.00; I2 = 0%). But the overall impact is uncertain and the efficacy and safety need to be evaluated[26].

In the case of anti-Xa agents, they have only small RCT that show LMWH better than UFH. So the quality of evidence is weak[27].

Prophylactic doses of heparin or low molecular weight heparin is recommended in non-bleeding patients with DIC that are critically ill[3,10,11].

But no directed evidence of the effects of anticoagulant has been found. The general practice in Thailand is not to use heparin prophylaxis.

Anticoagulant factor concentrates

Natural protease inhibitor

1) Antithrombin (AT)

Antithrombin (AT) is a natural anticoagulant important to inhibit over-activated coagulation and inflammation during sepsis. The activity of AT is decreased in the patient with DIC associated sepsis[28]. Most studies have been done in patients with sepsis, and a few in patients with DIC associated sepsis. Therefore, the recommended treatment is different from what is prescribed in the guidelines. RCT to evaluate the effect of antithrombin in patients with severe sepsis, have found no decreasing of mortality when comparing with placebo[29]. A systematic review to evaluate effect of antithrombin in DIC associated severe sepsis has found that antithrombin benefit in overall survival with the odds ratio for short-term all-cause mortality of 0.649 (95% confidence interval, 0.422-0.998)[30].

A recent study to evaluate the clinical efficacy of AT in low levels of AT patients has shown benefits. This study, conducted in Japan, is a non-randomized multi-institutional survey to evaluate 307 patients with septic DIC. Evaluation between two groups, and both groups have the AT activity less than 40%. They found a significantly improved rate of survival and recovery form DIC in the dose of 3,000 IU/day of AT concentration more than the dose of 1,500 IU/day of AT (77.1% vs. 56.4%; $p = 0.010$). The risk of bleeding did not increase[31]. But this study was not a RCT, so the antithrombin concentration is not recommended due to the absence of prospective evidence from RCTs to confirm the benefits[3,7].

2) Thrombomodulin (TM)

Thrombomodulin (TM) is a natural anticoagulant. It binds to thrombin and mediates the activation of protein C. A small retrospective study of DIC associated acute leukaemia, to evaluate outcomes between recombinant human thrombomodulin (rTM) and heparin, included 57 patients found benefits in efficacy and overall survival in the group of rTM ($p = 0.016$)[32].

3) Activated protein C (APC)

Activated protein C (APC) is a natural anticoagulant that plays a role in antithrombotic and anti-inflammatory agents among septic patients. Since 2001, the large RCT (PROWESS trial) study has found clinical efficacy of recombinant activated protein C (rhAPC) in DIC associated sepsis. There was a decrease in mortality rate in the rhAPC group when compared with placebo (24.7-30.8%)[33]. Another prospective trial has shown benefits in septic patients[34]. Later in 2012, a study of efficacy between Drofrecogin (DrotAA) was carried out. This study examined rhAPC with placebo in patients with septic shock (PROWESS-SHOCK randomized controlled trial, multicenter trial). The overall mortality rate did not increase. When the two groups were compared, the mortality at day 28 was 26.4% vs. 24.2% (relative risk in the DrotAA group, 1.09; 95% CI 0.92 to 1.28; $p = 0.31$). The mortality at day 90 was 34.1% in DrotAA group vs. 32.7% in placebo group (relative risk in the DrotAA group, 1.04; 95% CI 0.90 to 1.19; $p = 0.56$)[35]. This drug was withdrawn from sepsis treatment regimens. In conclusion, it is not recommended for patients who have severe sepsis and DIC.

Synthetic protease inhibitors

Synthetic protease inhibitors, such as gabexate mesilate and nafamostat, exhibit antagonistic effects on the kinin/kallikrein system, fibrinolytic system, complement system, and coagulation system, antithrombin activity. The studies in Japan have been found benefit in patients with DIC[36-38]. The Japanese DIC consensus (JSTH) recommends in bleeding, massive bleeding, and asymptomatic types of DIC[7]. But there is no randomized controlled trials (RCTs) showing any reductions in mortality or improvements in DIC. This medication is not used in Thailand.

Antifibrinolytic treatment

In generally, antifibrinolytic drug is not recommended in DIC patients. Except in conditions such as primary hyperfibrinolytic state induced DIC, and in patients that present with severe bleeding and could be treated with tranexamic acid (e.g. 1 g every 8 h)[3,7,10]. The 2011 and 2015 Cochrane reviews[39,40] evaluate treatment for DIC in patients with acute and chronic leukaemia. Since there were only four studies to evaluate, they cannot conclude whether there is benefit or risk in tranexamic acid, human APC, or recombinant human soluble TM. A large high quality trial is needed for evaluation.

Summary

The types of DIC are related to the underlying diseases. The diagnosis and treatment of DIC should

be considered on some types of DIC. The approach to treatment may be appropriate for some specific types of DIC, but not others. Thus, in the same clinical situation, the treatment should be based on individual patients; depending on clinical of thrombosis and/or haemorrhage. Future studies are needed to provide good quality of evidence for the treatment of DIC.

What is already known on this topic ?

We knew about clinical presentation, laboratory tests to diagnosis, and prognostic score of DIC. The treatment of DIC depends on the primary disease. Blood transfusion and anticoagulant should be used in DIC patients with clinical bleeding.

What this study adds ?

My review article shows that to determine the DIC subtype is very important to diagnose and treat DIC. Accordingly, to treat bleeding and massive bleeding types of DIC, blood transfusion should be considered. While treating the thrombotic type of DIC, anticoagulant should be considered. New therapeutic modalities such as anticoagulant factor concentrates and synthetic protease inhibitors have been recently studied and shown some success in the treatment. However, further good quality studies are needed.

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Potential conflicts of interest

None.

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การดูแลผู้ป่วยที่มีภาวะลิ่มเลือดแพร่กระจายในหลอดเลือด

นิศา มะเครือสี

ภาวะลิ่มเลือดแพร่กระจายในหลอดเลือด (Disseminated Intravascular Coagulation หรือ DIC) เป็นกลุ่มอาการที่เกิดจากการกระตุ้นกระบวนการแข็งตัวของระบบเลือด มีการผลิตทรอมบินเพิ่มขึ้น และทำให้เกิดความผิดปกติในหลอดเลือดในการทบทวนวิชาการครั้งนี้ใช้นิยามและการวินิจฉัยภาวะ DIC ที่อ้างอิงตาม International Society of Thrombosis and Haemostasis (ISTH) สำหรับการวินิจฉัยภาวะลิ่มเลือดแพร่กระจายในหลอดเลือดนั้นยังไม่มีการตรวจทางห้องปฏิบัติการที่เป็นมาตรฐานในการวินิจฉัย การวินิจฉัยในปัจจุบันอาศัยมีหลักฐานทางวิชาการที่น้อย ต้องอาศัยการตรวจทางห้องปฏิบัติการหลายชนิดและต้องมีการตรวจหลายครั้ง ปัจจุบันยังไม่มีหลักฐานทางวิชาการที่เป็นมาตรฐานชัดเจนในการรักษา หลักสำคัญคือต้องรักษาที่สาเหตุที่ทำให้เกิดภาวะนี้ ส่วนการให้ส่วนประกอบของเลือดได้แก่ พลาสมา และหรือเกล็ดเลือดนั้นให้ได้ถ้ามีข้อบ่งชี้ในผู้ป่วยบางราย