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Management of Disseminated Intravascular Coagulation in Emergency: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Disseminated intravascular coagulation (DIC) is life threatening disease it's often associated with sepsis, which require ICU management. In individuals with sepsis, the risk of DIC is especially high, DIC affects 30 to 50 percent of these individuals. Also it affects only about ten percent of patients with solid tumors, trauma, or obstetric emergencies. Hematological malignancies, aneurysms, and liver diseases can also cause the disease, the treatment for DIC focuses on resolving the

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underlying problem that led to this condition in the first place. As a result, antibiotics for severe sepsis, delivery in the case of placental abruption, and exploratory surgical intervention in the case of trauma are the pillars of DIC treatment, Patients with active bleeding or a high risk of bleeding, as well as those who require an invasive surgery, should consider platelet and plasma transfusions. Other anti-coagulant drugs can also be used. Prothrombin complex concentrates should only be administered in an emergency, due to their possible dangers. Recombinant human soluble thrombomodulin rhTM it was developed and licensed for clinical usage in Japan in 2008, and it's one of the novel treatments for DIC. Anti-Xa agents, Synthetic protease inhibitors, and antithrombin are another options for treatment. In this article we will be making overview of the disease, it's etiology an what's the current management options.

Keywords: Disseminated intravascular coagulation (DIC); ICU management; anti-coagulant drugs; recombinant human soluble thrombomodulin rhTM.

1. INTRODUCTION

Disseminated intravascular coagulation is a broad hypercoagulable state that can cause microvascular and macrovascular clotting as well as impaired blood flow, eventually leading to multiple organ failure syndrome. Disseminated intravascular coagulation is frequently associated with life-threatening diseases. The focus of treatment is on discovering and addressing the underlying cause [1].

Sepsis and septic shock are both types of systemic inflammatory and anti-inflammatory response syndrome, which can lead to life-threatening organ malfunction as a result of a serious infection. Disseminated intravascular coagulation is a common complication of sepsis and septic shock (DIC). Rangel-Frausto et al. found two decades ago that the prevalence of DIC complications increased as the severity of sepsis rose. In Japan, multiple studies have found that 50% of sepsis and septic shock patients treated in intensive care units (ICUs) also had DIC. Furthermore, patients with sepsis-induced DIC had a greater mortality rate than those without sepsis-induced DIC [2-8].

DIC can be caused by infections, solid tumours, haematological malignancies, obstetric disorders, trauma, aneurysms, and liver diseases, among other things, and each of these conditions has its own set of symptoms. These underlying etiological aspects must therefore be considered in the diagnosis and management of DIC. The underlying illness influences the type of DIC. The British Committee for Standards in Hematology, the Japanese Society of Thrombosis and Hemostasis, and the Italian Society for Thrombosis and Haemostasis have all published guidelines for the diagnosis and treatment of DIC in the literature. Although these three guidelines are largely comparable, there are some differences in the treatment recommendations for DIC [9-14].

This syndrome is linked to a significant risk of macro- and microvascular thrombosis, as well as a growing consumption coagulopathy that increases the risk of bleeding. DIC can be caused by a variety of pathological disorders, with sepsis, cancer, trauma, and obstetric catastrophe being the most common [15].

Coagulation problems commonly present themselves to emergency physicians as bleeding episodes or abnormal laboratory test results. At first, abnormal coagulation tests should be linked to a more distinguished diagnosis, while bleeding should be managed aggressively. Liver disease, vitamin K insufficiency, and disseminated intravascular coagulation are the most common causes of acquired coagulation disorders (DIC). Inhibitors, external influences like medications or extracorporeal circulation, and other disorders like amyloidosis are more uncommon [16].

2. ETIOLOGY

Several underlying conditions can cause disseminated intravascular coagulation (sepsis, cancer, trauma, and pregnancy complicated with eclampsia or other calamities). The cornerstone therapy techniques are treating the underlying ailment and eliminating the trigger mechanism. The goal of DIC-specific therapeutic treatments is to reduce blood coagulation activation and bleeding risk [15].

A systemic inflammatory reaction or the release of procoagulants into the bloodstream can cause disseminated intravascular coagulation in a variety of medical disorders. The pathological process of DIC is thought to occur in up to 30%

to 50% of instances of severe sepsis, which is the most prevalent cause of DIC. DIC has long been associated with sepsis caused by gram-negative bacteria, while the prevalence of this illness in sepsis caused by gram-positive bacteria may be similar. DIC can also be caused by other types of sepsis, such as parasites. DIC affects up to 20% of individuals with metastatic adenocarcinoma or lymphoproliferative illness, as well as one to 5% of people with chronic conditions such as solid tumours and aortic aneurysms. DIC has also been linked to obstetric difficulties include placental abruption, hemolysis, increased liver enzymes, and low platelet count (HELLP syndrome), as well as amniotic fluid embolism. Trauma, pancreatitis, cancer, snake bites, liver illness, transplant rejection, and transfusion reactions are some of the other causes of DIC. About 15.5 percent of DIC cases have also been connected to post-surgical problems [1,17-22].

3. PREVALENCE

DIC may occur in 30-50% of patients with sepsis, and it develops in an estimated 1% of all hospitalized patients. DIC occurs at all ages and in all races, and no particular sex predisposition has been noted [20,22].
In individuals with sepsis, the risk of DIC is especially high, DIC affects 30 to 50 percent of individuals, whereas DIC affects only about ten percent of patients with solid tumours, trauma, or obstetric emergencies [15].

Because standardized clinical grading systems for DIC are rarely consistently used in clinical practice, the overall frequency of DIC in hospitalized patients is unknown. Furthermore, the prevalence of DIC varies with hospitalization setting and is higher in severely sick patients admitted to intensive care units (ICUs). The frequency of DIC in this subset of patients varies between 8.5 percent and 34 percent, depending on the underlying illnesses and the diagnostic grading system utilized [15,23-27].

4. TREATMENT

The treatment for DIC focuses on resolving the underlying problem that lead to this condition in the first place. As a result, antibiotics for severe sepsis, delivery in the case of placental abruption, and exploratory surgical intervention in the case of trauma are the pillars of DIC treatment. Patients with active bleeding or a high risk of bleeding, as well as those who require an invasive surgery, should consider platelet and plasma transfusions. For actively hemorrhaging patients, a common platelet transfusion threshold is less than 50 x 100 platelets per litre, and 10-20 x 100 platelets per litre for individuals who are not bleeding but are at high risk of future bleeding. Fresh frozen plasma and cryoprecipitate can also be utilized to restore coagulation factors, often at a dose of 15 mL/kg to 30 mL/kg. Prothrombin complex concentrate is another option; however, this formulation only contains some coagulation components and will only help a patient's hemostasis to some extent. If a patient's clotting is severe, heparin may be required to prevent the clotting cascade from becoming activated again. Prophylactic anticoagulation with heparin or low molecular weight heparin (LMWH). should be given to DIC patients who are not actively bleeding Human activated protein C may also be useful in other situations, such as severe sepsis [1,28-31].

Prothrombin complex concentrates should only be administered in an emergency, due to their possible dangers. In both liver illness and coagulopathy caused by vitamin K insufficiency, adequate vitamin K substitution is recommended. The mainstay of DIC treatment is intensive treatment of the underlying illness. Substitution therapy is challenging, and it should be closely evaluated with appropriate laboratory tests. FFP is a good source of both procoagulants and inhibitors, although it can pose certain issues. Heparin therapy can be advantageous, however it is not commonly suggested [16].

5. ANTITHROMBIN

AT, like protein C and thrombomodulin (TM), is a physiological anticoagulant that is thought to inhibit 80% of the coagulation activity against thrombin and other coagulation factors. However, excessive thrombin generation, increased arterial permeability, deteriorated AT acceleration, and impaired AT synthesis in the liver all contribute to lower AT activity in sepsis-induced DIC. Reduced AT is linked to severe sepsis and a high death rate [2,32-38].

Several RCTs looked into the effects of high-dose AT treatment (18,000 U/5 days - 30,000 U/4 days) in patients with sepsis. In several studies, AT therapy was found to be effective in septic patients with low platelet counts and low AT activity. The KyberSept trial, the largest RCT, found that high-dose AT treatment did not reduce mortality and increased the frequency of bleeding problems in sepsis patients. However, a

subgroup analysis of the KyberSept study found that AT treatment dramatically reduced mortality in patients with sepsis-induced DIC while having no effect on bleeding complications [2,39-41].

6. RECOMBINANT HUMAN SOLUBLE THROMBOMODULIN

Physiological TM forms a thrombin–TM complex by binding directly to thrombin with a high affinity, limiting thrombin activity. Protein C is converted to activated protein C by the TM-bound thrombin complex, which binds to the protein C receptor on the surface of vascular endothelial cells. The importance of the thrombin–TM complex in activating protein C41 in regulating the coagulation and inflammatory processes cannot be overstated. After a Phase III RCT, rhTM was developed and licensed for clinical usage in Japan in 2008. rhTM has an active extracellular domain, can bind to thrombin, and can activate protein C, similar to how physiological TM acts on the surface of vascular endothelial cells. 43 When utilised at therapeutic plasma concentrations, rhTM was also demonstrated to have a distinct mode of action, in which thrombin production is reduced via activation of protein C rather than direct suppression of thrombin activity [2,42-45].

7. PLASMA AND PLATELET SUBSTITUTION THERAPY

In individuals with DIC who have consumption coagulopathy, replacement of coagulation factors and platelets may be necessary, especially if they have active bleeding or need an invasive surgery. Blood component delivery has never been proved to worsen disseminated coagulation activation in clinical or experimental trials [15].

Without high-quality data, platelet concentrate and fresh-frozen plasma (FFP) are indicated in patients with DIC who are bleeding or are at high risk of bleeding. The transfusion platelet threshold is determined by the clinical status of DIC patients. Platelet concentrate is commonly given to patients with DIC who have active bleeding and a platelet count of fewer than 50 100/L, or to non-bleeding chemotherapy patients who develop DIC and have a platelet count of less than 20 100/L. 103.The use of particular concentrates is another technique for coagulation factor replacement. Fibrinogen is the final substrate in the activation of blood coagulation and the production of thrombin, as well as a requirement for successful platelet aggregation. Treatment with fibrinogen concentrate may significantly reverse hemorrhagic diathesis in patients with fibrinogen levels less than 1.5 g/dL. The use of fibrinogen concentrates in the management of DIC-related bleeding, on the other hand, is mostly based on case reports [15].

8. ANTI-XA AGENTS

Both Fondaparinux and Danaparoid sodium inhibit Xa by activating AT. The use of Fondaparinux for the prevention of DVT after orthopaedic surgery is advised; however, there is limited evidence to support its use in critically ill patients and those with other types of DIC. In Japan, danaparoid sodium is used to treat DIC, despite the fact that no RCTs have shown any improvements in mortality or DIC resolution rates. There is substantial evidence to support the use of these medicines as DVT prevention. However, there is limited evidence to support their usage in DIC patients, and they are not indicated in those who have bleeding or significant bleeding [9].

i. Synthetic protease inhibitors

Gabexate mesilate and nafamostat, for example, are synthetic protease inhibitors with numerous roles, including antagonistic effects on the kinin/kallikrein system, fibrinolysis, complement system, and coagulation system. In Japan, gabexate mesilate and nafamostat are commonly used and investigated; nevertheless, no RCTs have shown any decreases in mortality or improvements in the rate of DIC resolution. These medicines are frequently used in patients with bleeding, major bleeding, and non-symptomatic DIC because they have modest anticoagulant and antifibrinolytic properties [9,46,47].

9. MANAGEMENT OF DIC ASSOCIATED WITH PLACENTAL ABRUPTION

Because it is linked to significant occurrences in both the mother and the newborn, such as intrauterine foetal death, cerebral palsy, obstetric critical hemorrhage, and uncontrollable bleeding, placental abruption should be carefully examined in perinatal therapy. When disseminated intravascular coagulation (DIC) is present, it is more likely to induce catastrophic bleeding, which may necessitate hysterectomy or multi-organ failure, leading to maternal mortality. As a

result, both hemostatic procedures and DIC treatment should be performed early to prevent the advancement of serious disorders. Health counseling for pregnant women, early diagnosis, early treatment, the construction of an emergency care system, and the provision of a mechanism for transfer to higher-level medical facilities should all be adopted to improve maternal and neonatal outcomes [48].

10. DISCUSSION

In a Study in Japan: 3000 patients with sepsis were treated in the ICU in Septic DIC trial, which used a nationwide Japanese multicenter registry. Half of the patients had sepsis complicated by DIC. Anticoagulants were used as DIC treatment in practically all of these individuals with sepsis worsened by DIC. Murata et al used the Japanese national administrative database to report the use of medications for sepsis-induced DIC from 2010 to 2012. Antithrombin and recombinant human soluble thrombomodulin were routinely utilized in both of these studies to treat sepsis-induced DIC in Japan. The frequency of heparin administration, on the other hand, varied substantially between the two investigations. The indications for heparin treatment in patients with sepsis-induced DIC were unclear in Murata et al's study, but they were clarified in the Japan-Septic DIC trial. Heparin medication was not used only for the treatment of sepsis-induced DIC in Murata et al's study. Treatment for DIC is not commonly available in other countries. Only 3% of sepsis patients received AT treatment, according to a survey that looked at an international sepsis registry that included 12,881 patients with sepsis treated in 276 ICUs in 37 countries from 2002 to 2005. [2,49-51].

In a randomized, double-blind phase IV trial, patients with severe sepsis were given LMWH, UFH, or placebo every 12 hours during DAA (24 IU/kg/h for 96 hours) infusion. When heparin was given concurrently with DAA, the 28-day mortality rate was marginally lower (28.3%), compared to the placebo group (31.9 percent). Heparin-treated patients had a significantly higher frequency of bleeding during the first 6 days of treatment than placebo-treated patients. Ischemic stroke was considerably more common in the group treated with DAA alone (1.3 percent) than in the group treated with DAA and heparin over the first 6 days (0.3 percent) [15].

The therapeutic use of rsTM was established in Japan because thrombomodulin expression is down-regulated during sepsis. Following that, in a randomized Phase 2b study, the efficacy of rsTM in sepsis-induced coagulopathy was investigated, and a nonsignificant mortality difference of 3.8 percent was discovered. 39 A international Phase 3 trial was done after this study, and the results have been published. 40 In 800 septic patients with coagulopathy, a nonsignificant mortality decrease of 2.6 percent was seen. Additionally, D-dimer, thrombin-antithrombin complex, and prothrombin fragment F1+2 levels, as well as platelet counts, improved.Yamakawa et al. conducted a meta-analysis that included the most recent Phase 3 study and found that rsTM reduced mortality by about 13%; however, the difference was not statistically significant. The therapy had no effect on serious bleeding problems. rsTM may become a possible treatment for sepsis-associated DIC pending solid results from prospective RCTs [52-55].

A meta-analysis of anticoagulant therapy trials in sepsis patients looked at 24 randomized controlled trials that looked at the efficacy and safety of AT, APC, TFPI, UFH, LMWH, rTM, gabexate mesilate, and TF antagonist in patients with DIC. Patients with sepsis-induced coagulopathy, defined as alterations in INR, platelet count, AT activity, and D-dimer levels, showed no reduction in overall mortality in a pooled analysis of these trials. However, compared to those who did not get any anticoagulant medication, there was a significant reduction in mortality in the group with sepsis-associated DIC as defined by either the ISTH or JAAM criteria who received any of the studied therapies. [15]

11. CONCLUSION

There’s no doubt that Disseminated intravascular coagulation (DIC) is life threatening disease, the standard of management of such disease is management of underlying issue that causing it which in many cases caused by sepsis. Blood Transfusion can be beneficial in most severe case. Although that the usage of certain anti-coagulant have been proven to beneficial. The usage of some didn’t prove of much difference in the mortality rate change. Newer drugs such as Recombinant human soluble thrombomodulin can play key role but further research is needed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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