Coagulation disorders in critically ill children admitted at pediatric Intensive Care Unit: A review article

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Abstract

Background: critically ill children usually show imbalances in hemostasis with risk of subsequent bleeding or pathological thrombosis. The abnormal hemostasis in intensive care ranges from thrombocytopenia only to intravascular disseminated coagulation.DIC is a clinicopathological syndrome described as systemic haemostatic activation resulting in excess microvascular thrombosis in both small and intermediate sized vessels causing organ dysfunction. The continued platelets and coagulation elements consumption during the activation of haemostatic system causes bleeding complications in those patients). The D-dimer assay is more specific and sensitive than other fibrin split products to detect DIC.

The aim of this review: describe coagulation profile of critically ill patients and evaluate its predictive value for the outcome.

Conclusion: Coagulation disorders are common among critically ill children, ranging from thrombocytopenia to more severe disorder such as disseminated intravascular coagulation.

Adequate early treatment strategies are crucial in reducing these patients' morbidity and mortality.

Keywords: critical illness, disseminated intravascular coagulation, mortality

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Introduction

Critical illness is any disease state, medical or surgical, which requires treatment in the unit of intensive care. Critical illness is frequently associated with sepsis, but other conditions such as severe trauma, the post-surgical state, pancreatitis, burn injury, ischemia and hemorrhage can produce the same clinical findings as microbial invasion, despite there is no infectious organism (**Sharma et al,2019).**

Systemic inflammatory response syndrome

It is defined as massive inflammatory host response tonoxious agents that leads to expression of excess inflammatory mediators which cause concomitant activation of coagulation system, fibrinolysis and anticoagulant pathways **(Rajagopal et al,2017).**

Sepsis is inflammatory systemic response with suspected source of infection. Sepsis with one or more end-organ failure is called severe sepsis and, with hemodynamic instability despite intravascular volume repletion is called septic shock **(Bone et al, 1992).**

The occurrence of changed organ functionin severely ill septic patients with failure to maintain hemostasis without intervention is recognized asmultiple organ dysfunction syndrome **(Bone et al, 1992).**

Inflammation and coagulation activation

During tissue damage and infection, coagulation pathway is activated. It is divided into two pathways that converge and ultimately cause the activation of thrombin with the subsequent cleavage of fibrinogen into fibrin.

The clotting pathway is started with extrinsic pathway in which there is exposure of tissue factor (TF) at the site of injury. The blood is exposed to TF either by cytokine-induced expression on endothelial cells or directly by the subendothelial matrix or activated monocytes. Platelets can produce their own TF near damaged vessel. TF acts as a cofactor when Factor VII is activated, which results in Factor X activation (factor Xa). Factor Xa links the V-factor and calcium and generates a complex prothrombinase which splits the prothrombin into the thrombin. **(Palta et al,2014).**

The intrinsic pathway is started with stimulation of factor XII, plasma kallikrein and kininogen which leads to stimulation of factor XI which then stimulates factor IX**(Mann et al,2006) and (Butenas et al,1997).**

The combination between stimulated factor IX and factor VIII (factor VIIIa) stimulates factor X. Stimulated factor X (factor Xa) links factor V (factor Va) and changes prothrombin to thrombin **(Palta et al,2014**).

The clotting pathway activation during inflammation is restricted by several factors. This is important because it prevents the uncontrolled induction of pro-coagulant mechanisms.

Three major anticoagulant pathways regulate activity of pro-coagulant mechanisms: antithrombin, tissue factor pathway inhibitor and the protein C/thrombomodulin system **(Griffin et al,2007).**

There are many evidences that there is widespread interference between inflammation and coagulation, which means that inflammation not results in the activation

of coagulation only, but also the coagulation significantly affects inflammatory activity(**Levi et al,2008**).

Coagulation disorders in critically ill children

Critically ill children usually show imbalances in hemostasis with risk of subsequent bleeding or pathological thrombosis **(Nair and Parker,2021).**

The conditions that are associated with abnormal hemostasis include disseminated intravascular coagulation, liver disease, massive transfusion syndromes, anticoagulant overdose, thrombocytopenia, and platelet dysfunction(**Levi and Schultz, 2010).**

1-Thrombocytopenia:

Thrombocytopenia isrecognized complication in PICU and causes platelet transfusions frequently **(Kaur et al,2015).**

Causes of thrombocytopenia among critically ill children are numerous, but usually, it develops because of decreased formation, increased utilization, destruction of platelet, abnormal sequestration or a combination of any or all of these (**Thachil and Warkentin,2017).**

Critically ill children who have persisting thrombocytopenia are at higher risk for prolonged bleeding manifestation, prolonged duration of hospital stay, and even mortality **(Agrawal et al,2008).**

Differential diagnosis of thrombocytopenia in ICU: sepsis, DIC, massive blood loss, thrombotic microangiopathy, heparin-induced thrombocytopenia and immune thrombocytopenia (**Levi and Schultz, 2010**).

2-Disseminated intravascular coagulation:

2.1-Definition:

DIC is a clinicopathological syndrome described as systemic hemostatic activation resulting in excess microvascular thrombosis in both small and intermediate sized vessels causing organ dysfunction(**Ogura et al ,2007**).The continued platelets and coagulation elements consumption during the activation of hemostatic system causes bleeding complications in those patients(**Levi et al,2009).**

The hemostatic derangement in children with DIC results from cumulative effects of hypercoagulation and hyperfibrinolysis. When hypercoagulation is the main process, organ dysfunction is the main clinical manifestation and this is commonly seen in infection and trauma **(Wada et al ,2014)** and **(Toh, Alhamdi,2013).**If hyperfibrinolysis is the dominant process, bleeding will be the primary manifestation, for example, in acutemyeloid leukemia. Consumptive coagulopathy with massive bleeding is detected when two processes are simultaneously activated **(Wada et al ,2014).**

DIC is still an independent organ failure and mortality predictor for septic patients **(Iskander et al,2013).**

2.2-Etiology:

Several disease states may lead to the development of DIC generally via one of the following two pathways:

-A systemic inflammatory response, leading to activation of the cytokine cascade and then activation of coagulation (eg, in sepsis or major trauma).

-Release of procoagulant material into the bloodstream (e.g., in cancer or crush brain injury).

-In some situations (e.g., major trauma or severe necrotizing pancreatitis), both pathways may be present.

Sepsis and trauma are the major causes of DIC followed by organ dysfunctions, cancers, toxins like snake bite, liver disease, and immunologic disorders (**Levi et al,2009).**

2.3-Diagnosis of DIC:

Clinical aspects

The DIC is either manifested by hemorrhagic features or thrombotic features or both (**Rajagopal et al,2017).**

The hemorrhagic features of DIC include bleeding venipuncture sites, oozing of blood from indwelling catheters, minimal trauma-related generalized ecchymoses, mucosal bleeding from gingiva or gastrointestinal tract, hematuria or unexpected bleeding around drain sites in postoperative states.

The thrombotic features of DIC include thrombophlebitis at unusual sites, renal impairment in the absence of other explanations, seizures consistent with the microcirculatory ischemia, skin necrosis, or grayish discoloration of finger tips, toes or ear lobes.

DIC may be asymptomatic with abnormalities in laboratory tests only and this type of DIC called pre-DIC (**Wada et al,2014).**

Laboratory tests

The diagnosis depends on existence of an underlying disorder, which is known to lead to DIC combined with diagnostic laboratory tests.

The laboratory tests usually used are platelet count, coagulation profile, serum fibrinogen and fibrin split products or D-dimer.

Prothrombin time, partial thromboplastin time, platelet count and fibrinogen provide important clue on the procoagulant system, while D-dimer measure fibrin formation and fibrinolysis **(Levi et al,2009).**

The thrombocytopenia, prolonged coagulation tests, lowering in fibrinogen level and elevation in the D-dimer values all point towards extreme coagulation stimulation (**Veldman et al,2010**).

Fibrin (fibrinogen)-degradation products (FDPs) are protein fragments of various sizes that result from the proteolytic action of plasmin on fibrin or fibrinogen.

Plasma levels of these fragments are commonly increased in association with DIC in which their presence is of considerable diagnostic significance **(Rodgers and Lehman, 2013).**

D-dimer is special degradation product of fibrin. It is recognized in blood of patients with various thrombotic and thrombolytic

disorders **(Moresco et al,2003).**The D-dimer levels increase in cases with sepsis, venous thromboembolism, syncope, heart failure, trauma, and cancer **(Lippi et al,2014).** D-dimer is more specific and sensitive than other fibrin split products to detect DIC.

D-dimer is simpler, specific and sensitive in many laboratories than less sensitive tests for DIC(**El-Nawawy et al,2004).**

2.4-Management of DIC:

DIC management is based on the therapy of the underlying illness**(Rodger,2000).**

Additional helpful therapies may consist of blood products transfusion, fractionated plasma of purified coagulation factor concentrate, Anti-fibrinolytic agents, administration of physiologic coagulation inhibitor or anticoagulant strategies **(Levi and Schultz, 2010).**

Success in the management of DIC depends largely on whether the cause can be removed and on the quality of general medical care offered.

Early diagnosis and management of DIC in intensive care units of children could have an impact on the prognosis.

Blood products transfusion

Platelets, cryoprecipitate and fresh frozen plasma are commonly used blood products in DIC.

Plasma transfusion should be kept for bleeding patients with DIC and the decision should not be built on laboratory abnormalities alone.

Platelet transfusion is given to patients with platelet count<30-50x109/L accompanied with bleeding or at high risk for bleeding, and is given in platelet count <10x109/L, regardless of the presence or absence of bleeding.

Cryoprecipitate is used in bleeding patients when fibrinogen level is <1.5 g/L **(Wada et al,2014).**

Purified coagulation factor concentrates

Prothrombin complex concentrate is a source of blood clotting factors(II, VII, IX and X).

Recombinant factor VIIa was reported to be used in major bleeding due to surgery or trauma.

The coagulation factor concentrates are indicated when transfusion of big volumes of plasma is harmful to patients.

Anticoagulants—heparins

The therapeutic dose of heparin should be administered in DIC with predominant thrombosis.

The unfractionated heparin use is contraindicated when there is evidence of bleeding **(Levi et al,2009).**

Anti-fibrinolytic agents

The anti-fibrinolytic agents as tranexamic acid may also be supportive in the prevention or treatment of bleeding, in particular if hyper-fibrinolysis is believed to be the major contributor to hemostatic defect.

Physiologic coagulation inhibitors

Protein C is low in septic patients and restoration of PC has been suggested to reduce the severity of DIC**(Morley,2016).**

Anti-thrombin (AT) is reduced during excess thrombin formation in DIC(**Toh and Alhamdi,2013).**

AT replacement is not widely recommended in pediatric DIC although AT treatment in adults has demonstrated significant decrease in mortality **(Oren et al,2005).**

Thrombomodulin is a vascular endothelial glycoprotein, which binds to thrombin and promotes PC activation. Activated PC with PS inhibits factor Va and actor VIIIa to avoid thrombin generation. The recombinant form of thrombomodulin has similar pharmacological action as APC (**Yagasaki et al,2012).**

Conclusion

- Coagulation disorders are common among critically ill children, ranging from thrombocytopenia to more severe disorder such as disseminated intravascular coagulation.
- Adequate early treatment strategies are crucial in reducing these patients' morbidity and mortality.

Summary for coagulation disorders in critically ill children admitted at pediatric intensive care Unit:

1-Critical illness is any disease state that requires treatment in the unit of intensive care as in sepsis, severe trauma, the post-surgical state, pancreatitis, burn injury, ischemia and hemorrhage.	**(Sharma et al,2019).**
2-Systemic inflammatory response syndrome is massive inflammatory host response to noxious agents with concomitant activation of coagulation system, fibrinolysis and anticoagulant pathways.	**(Rajagopal et al,2017).**
3- Critically ill children usually show imbalances in hemostasis with risk of subsequent bleeding or pathological thrombosis.	**(Nair and Parker, 2021).**
4- Thrombocytopenia is a recognized complication in PICU and causes platelet transfusions frequently.	**(Kaur et al,2015).**
5- Disseminated intravascular coagulation is clinicopathological disorder characterized by excessive generation of microvascular thrombosis leading to organ dysfunction and continued platelets and coagulation elements consumption leading to bleeding complications.	**(Ogura et al ,2007) and (Levi et al,2009).**
6- D-dimer is simpler, specific and sensitive in many laboratories than less sensitive tests for DIC.	**(El-Nawawy et al,2004).**

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