Chapter

Protocols for Bleeding and Thrombosis in Pediatric Intensive Care Units

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Abstract

Bleeding and thrombosis are the common hematological complications found in children who are admitted in the pediatric intensive care units (PICUs). Some of those complications could be mild, however some could be serious or life-threatening for critically-ill children. The etiologies of those conditions could be due to the underlying diseases, i.e., congenital bleeding disorders, complications of the diseases, i.e. coagulopathy due to disseminated intravascular coagulation (DIC), and also the side effects from the treatments themselves, i.e., massive transfusion or extracorporeal membrane oxygenation (ECMO). Early detection and management and prevention of those complications could decrease the morbidity and mortality of the children in PICUs. Although most guidelines of management of those bleeding and thrombosis in adults is well established, the evidences for the management of those conditions in children are limited. In addition, developmental hemostasis during the childhood, which is different from adulthood, could challenge the management of those conditions in children admitted in PICUs.

Keywords: pediatrics, intensive care unit, massive transfusion, extracorporeal membrane oxygenation, thromboprophylaxis

1. Introduction

Pediatric patients who are admitted in pediatric intensive care units (PICUs) are at risk of having bleeding and thrombotic complications due to several factors including their underlying diseases, the medications and procedures they received during the admission and the current conditions of the patients that lead them to be admitted in PICUs [1]. Since the hemostasis in children are different from the adults, management of bleeding and thrombosis in pediatric patients is challenging and may not be directly adopted from the evidences in adult patients. Moreover, developmental hemostasis should be taken into accounts of management. This chapter includes massive transfusion, extracorporeal oxygen membrane oxygenation (ECMO) and venous thromboembolism (VTE) protocols in children based on current evidences.

2. Developmental hemostasis

The hemostasis is a group of system which is responsible for the bleeding control after a vascular injury and also recanalization of that vessel when the bleeding is stopped. The balance between the bleeding control, which is the interaction between primary and secondary hemostatic systems, and the recanalization process, including anticoagulation and fibrinolytic systems, is crucial to maintain normal hemostasis in the body [2, 3] The summary of normal hemostatic system is shown in **Figure 1**. The defects in the bleeding control cause bleeding disorders while the impairment of recanalization process lead to thrombotic disorders.

As same as other systems in the human body, the hemostatic system has been changed from the neonatal period to the adulthood in all parts of hemostatic system. The summary of developmental changes in hemostatic system in summarized in **Table 1**.

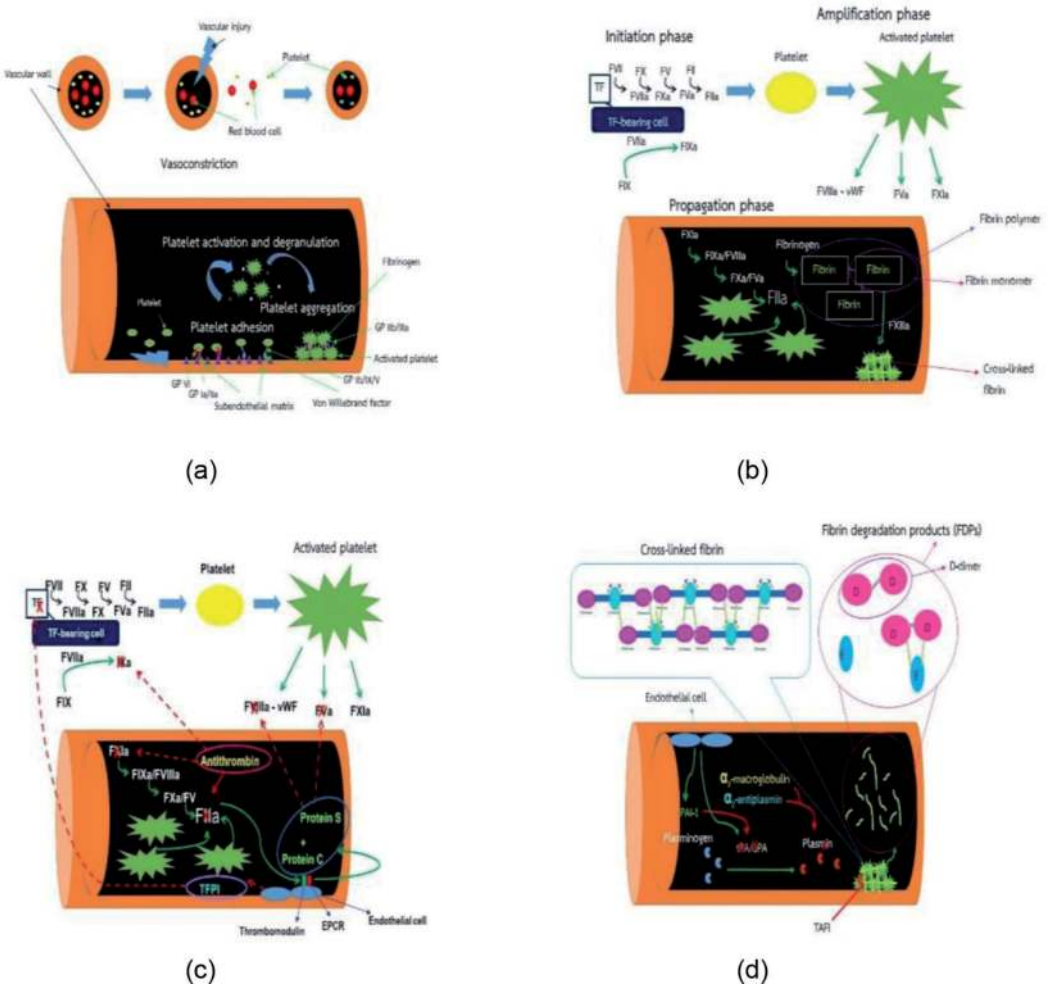

Figure 1.
The summary of normal hemostatic system. (a). Primary hemostasis. (b). Secondary hemostasis. (c). Anticoagulation system. (d). Fibrinolytic system.

Hemostatic system	Comparison between children and adults
Primary hemostatic system	• *Vessel wall and endothelial cells:* ○ Elevated glycoaminoglycans in vessels of neonates leading to increased antithrombotic property by working with antithrombin (AT) ○ Increased von Willebrand factor (VWF) and large VWF multimers from endothelial cells • *Platelets:* ○ Platelet numbers in term neonates = those in children and adults but may decrease in preterm neonates ○ Platelets in term neonates express low receptors on platelet surface resulting in less platelet response ○ High red cell mass, mean corpuscular volume (MCV), VWF and elevated proportion of large VWF multimers
Secondary hemostatic system	• Vitamin K-dependent factors (prothrombin, FVII, FIX and FX), contact factors and FV < adult levels • FVIII, VWF and tissue factor (TF) levels > adults in first 6 months of life • Fibrinogen, FV and FXIII = adult levels
Anticoagulation system	• Protein C (PC), protein S (PS), AT and tissue factor pathway inhibitor (TFPI) < adult levels
Fibrinolysis system	• Plasmin, plasminogen activator inhibitor (PAI)-1 and α_2-antiplasmin (AP) < adult levels • tissue plasminogen activator (t-PA) and α_2-macroglobulin (M) > in adult levels
Net hemostasis	• Endogenous thrombin potential (ETP) almost 2-time in neonates than adults

Table 1.
The summary of developmental changes of hemostasis [4, 5].

2.1 Massive transfusion protocol in children

In adult patients who undergo major surgeries or experience traumas, massive transfusion is defined by transfusion of blood components particularly red blood cell concentrate (RBC) equal or more than 10 units within 24 hours, receiving RBC more than 4 units in 1 hour or requirement of blood components more than 50% of total blood volume within 3 hours [6]. Although the definition of massive transfusion in children is unclear, some studies defined receiving transfusion volume of blood components more than 40 ml/kg within 24 hours as massive transfusion [7]. Moreover, adoption of adult's definitions of massive transfusion is not practical in pediatrics as some may not survive long enough to fit with those definitions. Moreover, Acker et al. showed that the adoption of assessment blood consumption (ABC) scale of adults in children had less sensitivity and specificity than those when it was studied in adult population [8]. Although the current proposed definition of pediatric massive transfusion is transfusion of blood components more than 37 ml/kg within 4 hours to make the diagnosis and initiate the intervention sooner [7], more studies are required to confirm the benefits of this definition.

The main mechanisms of massive transfusion consist of severe tissue injury from the surgery or trauma which releases abundant mount of tissue factor (TF) which

massively activated coagulation cascades and hemodilution of the inappropriate resuscitation with intravenous fluid and blood components. Those subsequently lead to a vicious cycle of progressive coagulopathy, acidosis and hypothermia which results in ongoing bleeding and multiorgan failure [6].

When the pediatric patients reach the definition of massive transfusion, the activation of the massive transfusion protocol (MTP) should be commenced. Currently, most MTPs are driven by blood components ratio protocol. The common MTPs suggest 1:1:1 ratio of fresh frozen plasma (FFP): RBC: platelet concentrate (PC) [10]. However, the most effective ratio between FFP and RBC is still controversy. Cunningham et al. reported that high (≥ 1: 1) FFP: RBC ratio, associated with better survival outcome at 4 and 24 hours than medium (≥ 1:2 to <1:1) and low (< 1:2) FFP: RBC ratios (P = 0.02). The survival outcome of medium PC: RBC ratio was higher than high and low ratios of PC:RBC without statistical significance [9]. In addition, Diab et al. recommended ratio of FFP:RBC:PC or cryoprecipitate (cryo) at 1:1:2 for massive transfusion in children [6]. However, the systematic review by Maw and Furyk showed minimal benefit of fixed ratio of FFP: RBC: PC at 1:1:1 in pediatric massive transfusion [10]. Though all blood components are derived from the whole blood (WB), hematocrit, platelet count and coagulation factors are higher in WB and lower volume than each separated blood component [7]. Furthermore, a few studies showed faster access with similar safety and clinical outcomes of using WB for resuscitation in children [11, 12].

Besides fixed ratio of blood components protocol for massive transfusion, thromboelastography (TEG) and rotational thromboelastometry (ROTEM), the viscoelastic test to measure global hemostasis and currently used as a point-of-care testing [POCT], have been used as a guided tool for management of massive transfusion [7, 10, 13]. The systematic review of using TEG or ROTEM to measure hemostasis in adults and children revealed lower dose of transfused blood components and decreased mortality than the fixed ratio for massive transfusion in patients with bleeding [13].

Other adjunctive treatments of massive transfusion include tranexamic acid (TXA) and recombinant activated factor VII (rFVIIa). Tranexamic acid, a lysine analogue, is an antifibrinolytic agent which inhibits plasminogen activation and prevent fibrinolytic process [7]. The pediatric trauma and tranexamic acid study (PEDTRAX) revealed TXA significantly decreased mortality rate (odds ratio 0.3) without increasing thromboembolic (TE) and cardiovascular events in pediatric population [14]. rFVIIa, a bypassing agent, which is used for bleeding control in both hemophiliac A and B patients who have inhibitor to factor VIII and IX, respectively [15]. The systematic review by McQuilten et al. showed no benefit of the decreased mortality for the off-label use of rFVIIa in massive transfusion and there was an increased risk of TE, particularly arterial TE, in patients using rFVIIa, therefore, routinely using rFVIIa as a part of MTP is not recommended [16].

2.2 Extracorporeal oxygen membrane oxygenation (ECMO) protocol in children

ECMO is an equipment used for cardiopulmonary support in children who have severe cardiac and/or pulmonary compromise and do not respond to medications and mechanical ventilatory support. There are two types of ECMO, venovenous (VV) ECMO which mainly support respiratory system while venoarterial (VA) ECMO support both respiratory and cardiac system [17–19]. To maintain the blood flow of ECMO circuit, which is an artificial system with nonbiological surface, the usage of an anticoagulant, mainly unfractionated heparin (UFH), is required to reduce thrombin

and fibrin formation in the ECMO circuit. The current guideline for ECMO management is recommended by Extracorporeal Life Support Organization (ELSO) registry which is the largest international adult and pediatric database for patients treated with extracorporeal life support (ECLS) [19]. There are four parts of ECMO circuit including a cannula, a pump with console, an oxygenator and a heart exchanger [20].

Monitoring and adjustment of the UFH dosage to balance between bleeding and clotting in patients using ECMO is challenging [21]. Dalton et al. reported the high bleeding complication in children receiving ECMO at 70% including 16% of intracranial bleeding. In contrast, 31% of children required ECMO circuit components changes due to clot and 13% of children developed patient-associated clot [22]. Although the standard dose of UFH for ECMO is the treatment dose of UFH at 20–25 unit/kg/hour, the variation of dose could be increased to 50–60 unit/kg/hour to reach the target ranges of UFH monitoring [23]. The summary of methods for UFH monitoring with the target ranges of each methods is shown in **Table 2**. However, the target ranges can be varied based on the institutional protocol, normal laboratory reference range of each test and the current bleeding conditions of the patients and thrombotic status of both patients and ECMO circuits. Moreover, there is currently no one perfect laboratory test to monitor UFH when the children are receiving ECMO.

Antithrombin (AT) is a natural anticoagulant and the main targeted protein working UFH to inhibit FXa and thrombin [23]. Therefore, the effect of heparin can be decreased by the deficiency of AT or heparin resistance particularly in infants aged less than 6 months when the synthesis of AT is not fully developed [21, 27]. Although the targeted AT level while the patients are receiving ECMO is approximately 70–120% [21, 28], there is no current consensus on that targeted AT level, the dosage, the timing and method of administration even in adult patients [28]. Moreover, the impact of AT supplementation in patients receiving ECMO is less understandable than that in patients with hereditary AT deficiency due to the patient and circuit interaction and their underlying diseases [21]. Furthermore, the widely available source of AT is FFP which is not appropriate source of AT and the AT concentrate, both plasma-derived and recombinant products with various properties of each product, can be accessible only in some countries [21].

In children who have contraindication of using UFH such as heparin-induced thrombocytopenia (HIT) or heparin resistance [21], bivalirudin, an intravenous direct thrombin inhibitor which inhibit both circulating thrombin and clot bound thrombin [29] could be an alternative anticoagulant for children receiving ECMO [23]. The median loading dose of bivalirudin is 0.1–0.125 mg/kg and the maintenance dose between 0.045 and 0.48 (0.125) mg/kg/hour [27, 30] to keep targeted APTT between 45 and 85 sec [23, 27]. However, unlike heparin, no antidote is available for bivalirudin and dose reduction is needed in children with renal disease as the main clearance organs are kidney and liver [23, 27].

2.3 Venous thromboembolism (VTE) prophylaxis in children

The incidence of VTE in children has been increasing during the last two decades in both Western and Asian countries especially in hospitalized children [31–33]. Even though the guideline for VTE thromboprophylaxis is well established in adult population [34, 35], the statement of VTE prophylaxis is not clearly mentioned with the limited available evidences and various details of the study [36–38].

Apart from pediatric patients who have hereditary thrombophilia, the hospitalized children are at risk of development of TE since two of three most common risk factors

Methods	Blood sample for testing	Target ranges	Advantages	Drawbacks
Activated clotting time (ACT)	Whole blood	150–170 sec	•POCT •Less amount of required blood volume •Measurement of whole blood clotting	•Difference between operator •Specific to each analyzer and reagent •Results interfered by platelet defects, other coagulopathy, hypothermia and hemodilution
Activated partial thromboplastin time (APTT)	Plasma	60–90 sec 40–60 sec in patients with bleeding risk	•Widely available •Ability to defect other etiologies of coagulopathy by using heparinase	•Specific to each analyzer, method of measurement and reagent •Different normal reference range for age •More amount of required blood volume •Results interfered by UFH contamination in the sample, other coagulopathy, hypothermia and hemodilution
Anti-activated factor X (anti-FXa)	Plasma	0.2–0.7 (0.3–0.7) units/mL	•Direct measurement of UFH effect of inhibition of FXa	•More amount of required blood volume •Not widely available •Required an experienced staff •Higher cost •Slower turnaround time •Results interfered by increased bilirubin, triglyceride and plasma free hemoglobin
TEG and ROTEM	Whole blood	No definite cutoff	•POCT •Measurement of whole blood clotting •Global hemostatic test •Ability to monitor other anticogulant	•No standardization •No definite cutoff especially in children [26] •Requirement to concomitantly interpret with other tests

POCT, point-of-care test; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

Table 2.
The summary of methods for UFH monitoring with the target ranges of each methods [21, 23–25].

of VTE in the previous reports, including central venous catheterization (CVC), immobilization more than 72 hours and oral contraceptive pill (OCP), are frequently found in pediatric patients who are admitted in the hospital especially children admitted in PICU [37]. Moreover, the incidence of VTE is more common in neonates and adolescents [39], hence, most VTE prophylaxis study protocols were mainly included children admitted in PICU and adolescents to prevent VTE in risky patients.

Recently Jaffrey et al. reported the new score to assess the risk of VTE development in hospitalized children including Braden Q mobility score, length of stay, CVC, history of congenital heart disease and autoimmune/inflammatory disorders in the

risk assessment model (RAM) in 395 pediatric patients with the area under the curve (AUC) of 0.78 [40].

The methods to prevent VTE in children consist of physical methods e.g. intermittent pneumatic compression (IPC), graduated compression stockings (GCS) and devices and venous foot-pumps (VFPs) and pharmacological methods including oral and parenteral anticoagulants [36]. Even though the physical methods do not put the patients to be at risk of bleeding episodes, those could be applied realistically in larger children who usually weigh more than 40 kg [36]. Pharmacological prophylaxis is suggested for only children who have multiple risk factors of VTE [36] and this method should be balance with the bleeding risk of the patients. Children who require CVC, the heparin-bonded central venous line is suggested if it is available [41] due to no thrombosis was found in the report by.

3. Conclusions

Establishing the protocols for hemostatic control in children is very challenging due to the developmental hemostasis which make the adoption of adult protocols may not be the appropriate way. Since the evidences of hemostasis management protocols for children admitted in PICUs are still limited, more studies in this field should be warranted to close the knowledge gap and able to guide the better and more effective practice for pediatric patients in the future.

Conflict of interest

The authors declare no conflict of interest.

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