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Management of Dilutional Coagulopathy during Pediatric Major Surgery

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Keywords
Blood loss · Blood products · Blood transfusion · Colloids · Hemodilution · Hemostatic disorder · Perioperative · Pediatric anesthesia

Summary
Perioperative dilutional coagulopathy is a major coagulation disorder during adult and pediatric surgery. Although the main underlying mechanisms are comparable, data of the development and management of dilutional coagulopathy in children are scarce. Observational data showed that intraoperative coagulation disorders mainly based on complex disturbances of clot firmness including acquired fibrinogen as well as factor XIII deficiencies, while clotting time and platelet counts remained fairly stable. A fast and reliable monitoring of the entire coagulation process (e.g. thrombelastometry) might be of extreme value for detection and guidance of effective coagulation management. Although the transfusion of fresh frozen plasma was recommended in several guidelines, the use of coagulation factors might offer an alternative and potentially superior approach in managing perioperative coagulation disorders. Further studies are urgently needed to determine the efficacy of modern coagulation management.

Schlüsselwörter
Blutverlust · Blutprodukte · Bluttransfusion · Kolloide · Hämodilution · Hämostatische Störung · Perioperativ · Pädiatrische Anästhesie

Zusammenfassung
Das Auftreten einer Dilutionskoagulopathie im pädiatrischen operativen Bereich ist ein klinisches relevantes Problem. Eine schnelle und zuverlässige Laboranalyse ist für die Diagnosesicherung und Steuerung der Therapie von besonderer Bedeutung. Viskoelastische Methoden wie das ROTEM® oder TEG® scheinen hierfür besonders geeignet zu sein. Der erworbene Fibrinogen-Mangel ist regelmässig bei Auftreten einer Dilutionskoagulopathie zu diagnostizieren und kann optimalerweise mittels Fibrinogenkonzentrat therapiert werden, wobei nicht endgültig geklärt ist welcher perioperative Grenzwert für den Fibrinogen-Spiegel angestrebt werden sollte. Die Substitution anderer Gerinnungsfaktoren (z.B. Faktor-XIII-Spiegel < 60%) sollten ebenfalls auf laborchemischen Analysen basieren. Die Transfusion von gefrorenem Frischplasma (FFP) erfolgt in einer Dosis von 30 ml/kg im Rahmen einer Massivblutung, sollte jedoch erst erwogen werden, wenn andere gerinnungsbeeinflussende Faktoren optimiert wurden (z.B. Fibrinogen-Mangel, Hyperfibrinolyse, Azidose, Hypothermie, Thrombozytopenie oder Thrombozytopathie). Basierend auf aktuellen Empfehlungen kann der routinemäßige Einsatz von rekombinantem Faktor VIIa nicht empfohlen werden. Im Gegensatz dazu hat die Anwendung von Antifibrinolytika signifikant zur Reduktion des intraoperativen Blutverlusts und des Bedarfs an Bluttransfusionen bei nichtherzchirurgischen pädiatrischen Eingriffen beigetragen. Weitere kontrollierte Studien zur Evaluierung effektiver und sicherer laborbasierter Strategien zur Therapie der Dilutionskoagulopathie sind notwendig.

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Introduction

The causes of dilutional coagulopathy are complex, and both pro- and anticoagulant pathways are affected; but the underlying mechanisms are not fully understood. In terms of laboratory changes, it seems to be comparable to hemostatic changes during major hemorrhage following trauma injury [1].

Occurrence of generalized microvascular oozing in patients requiring massive transfusion was first described by Counts and colleagues in 1974 [2]. They found platelet count and fibrinogen level to be most useful laboratory tests for predicting abnormal bleeding and guiding therapy. The prothrombin time (PT) and partial thromboplastin time (PTT) were shown to correlate with generalized bleeding only if they were markedly prolonged. This observation was supported by retrospective analysis of 172 surgical patients undergoing massive transfusion that was published 3 years later [3]. However, in that study administration of platelet concentrates and/or fresh frozen plasma (FFP) without evaluation of hemostasis failed to decrease the requirements of whole blood and/or packed red cells. The authors concluded that a directed intervention after identification of the underlying disorder is likely to be more effective. In 1987, Ciavarella and colleagues [4] recommended initial treatment by transfusion of platelet concentrates in massive transfusion setting. That study group recommended supplemental FFP or cryoprecipitate if the fibrinogen level is less than 0.8 g/l. After major change in the treatment of massive blood loss in the 1990s towards pure component therapy and the use of plasma-poor packed red cells instead of whole blood, Hiippala and co-workers [5] were able to demonstrate for the first time that deficiency of fibrinogen develops earlier than any other hemostatic abnormality when plasma-poor red cells are used for the replacement of major blood loss in surgical patients. This observation was supported by more recent investigations focusing on the importance of acquired fibrinogen deficiency that seems to be the leading determinant in dilutional coagulopathy [6–10]. In addition, more recent data points toward the importance of factor XIII (FXIII) in clot stabilization during major surgery and consecutive blood loss [11].

Today, dilutional coagulopathy is usually defined as loss, consumption, or dilution of coagulation factors and occurs when blood is replaced with fluids that do not contain adequate coagulation factors [12]. Depending on the amount and the type of fluid replacement, dilution of cellular components and coagulation factors were inevitable. Based on the dynamic of blood loss and consequently loss and consumption of factors a clinical relevant dilution coagulopathy occurs constantly [13]. Moreover, disturbance of hemostatic potential might be further deteriorated by hypothermia, acidosis, and fibrinolysis, thus leading to worsening of patient's outcome [14]. If a critical threshold of plasma concentration of coagulation factors was reached, bleeding will be further perpetuated. The incidence of dilution coagulopathy was decreased by preparation of modern (nearly plasma-free) autologous blood products. In contrast to congenital bleeding disorders based on single coagulation factor deficiency, dilutional coagulopathy is related to multifactorial changes that affects thrombin generation, clot firmness, and fibrinolysis [15]. Therefore, it seems hard to predict if the complex interaction of cellular components, pro- and anticoagulant factors, and fibrinolytic activators and inhibitors will finally form a stable clot during moderate to severe hemodilution.

Diagnosis of Dilutional Coagulopathy

Unfortunately, routine plasmatic coagulation tests are of limited help for timely management of perioperative bleeding due to long turnaround times, insufficient differential diagnosis of complex acquired intraoperative coagulopathy, and insensitivity for function of fibrinogen, hyperfibrinolysis and platelet dysfunction [16]. Another meaningful limitation is that measurement of fibrinogen levels using the photometric Clauss assay can be considerably altered after massive fluid resuscitation and that colloids may induce erroneously increased levels of fibrinogen [16, 17].

Rotation thrombelastometry (ROTEM®, AxonLab, Baden, Switzerland) offers an alternative approach to assess perioperative coagulation disorders by means of viscoelastic testing [18]. First results are available only 10 min after starting with testing and clot formation can be online observed by a bedside monitor. Data on the effective use of the ROTEM were published from adult liver transplantation [19], adult trauma patients [20], and intraoperative coagulation management in children [21, 22]. Notably, a normal ROTEM trace showed high negative predictive value and was suggested to early identify surgical bleeding by distinguishing it from coagulopathic bleeding [23]. Additionally, both devices were stated as golden standard for detecting hyperfibrinolysis, which may have deleterious impact on mortality. However, there is a lack of data proving the usefulness of a ROTEM-guided coagulation management in children and clinically meaningful trigger levels for initiating coagulation therapy.

Clinical observations have shown that intraoperative changes in hemostasis showed early signs of moderate to severe acquired hypofibrinogenemia as well as marked decrease in FXIII levels, while platelet count remained fairly stable [24]. In a retrospective analysis of 150 children with craniofacial surgery 33 experienced severe hypofibrinogenemia with levels ≤ 100 mg/dl, while only 2 children showed platelet count ≤ 50,000/μl [25]. Throughout the surgical procedures children typically met the traditional laboratory criteria for dilutional coagulopathy (PT and activated partial thromboplastin time (aPTT) prolonged more than 1.5 times) while recent data showed no relevant changes as displayed in the ROTEM coagulation time (CT) [26]. Similar findings of other investigator groups [27–29] supported the modest correlation between

ROTEM CT and PT or aPTT. Therefore, results of the clotting time in the ROTEM and results of PT or aPTT cannot be interchangeably used for detecting intraoperative hemostatic disorders. Based on results of the ROTEM, it may be concluded that currently recommended thresholds for PT/aPTT might overestimate the need for coagulation therapy, or, in other words, coagulation measurement of the entire process of clot formation started with thrombin generation (PT/aPTT) with close interaction to clot strength (fibrinogen) and final lysis. In contrast, ROTEM FibTEM A10 and MCF showed very high correlation to plasma fibrinogen levels. In addition, recently published data support the fact that the mechanical detection principle of fibrinogen testing seems to be more reliable than photometric techniques [17]. However, there are some important limitations that need to be considered when interpreting ROTEM results: inability to detect von Willebrand syndrome, platelet function disorders, or drug monitoring (e.g. vitamin K anatagonists) [16].

There was a clear advantage for ROTEM as compared to standard coagulation test concerning extensively shorter turnaround times, which will have impact on a timely and more targeted coagulation therapy [30–32].

Influence of Colloids on the Development of Dilutional Coagulopathy

Another important aspect of developing dilutional coagulopathy is the use of colloids and the combined interaction with hemostasis. There is fair evidence that colloids, especially high molecular solutions and dextrans, were linked to severe disturbance of clot formation [6, 33, 34]. By manufacturing new low molecular starches, impact on clot formation was significantly reduced, but depending on the amount of fluid given a marked impairment of hemostasis can be observed [35]. The negative impact can be specified as fibrin polymerization interaction with a consecutive distinct weakening of the clot. Additionally, specific interaction with von Willebrand factor (VWF) / FVIII and platelets were observed (e.g. von Willebrand-like syndrome) [33]. Even a colloid-mediated increase in fibrinolytic tendency by α_2-antiplasmin-plasmin interaction was observed that may alter clot firmness [36–37].

As in adults, the use of colloids showed similar changes of the hemostatic profile in the pediatric population. The influence of colloids on hemostasis was investigated in a prospective trial in small children (3–15 kg body weight) who randomly received a bolus of 15 ml/kg of either albumin 5%, 4% modified gelatin solution or 6% hydroxyethyl starch (HES 130/0.4) after induction of anesthesia [38]. Fibrin polymerization as measured with the ROTEM FibTEM test was significantly decreased in all groups, but most pronounced in the HES group. In contrast, no relevant changes in the coagulation time that represents the phase of thrombin generation were observed. Notably, mean FXIII concentrations of <60% were obtained in all groups after volume administration. A multicenter trial in 81 children aged < 2 years who underwent noncardiac surgery showed no significant differences in hemodynamics, coagulation parameters, or blood loss if comparable amounts of 6% HES (130/0.4) or albumin 5% were used for perioperative fluid resuscitation [39]. However, to date no conclusive statement can be made which type of fluid should be used to stabilize hemodynamics in children but having no relevant effect on hemostasis.

Management of Dilutional Coagulopathy in Children

It should be recognized that several publications investigated coagulopathies in the clinical setting of cardiac surgery. However, if cardiac bypass was used, additional disturbance of the coagulation system, such as platelet dysfunction, excessive fibrinolysis and consumption of coagulation factors, might aggravate dilution following administration of the priming volume [40]. Thus, coagulation testing and management should be adapted to the type of surgery.

A modern concept of bleeding therapy should be adapted to local conditions and could consist of a bedside coagulation testing (e.g. ROTEM), targeted administration of purified coagulation factors leading to fast responsiveness, and calculable increase in those factors that were critically decreased [16]. It needs to be mentioned that reference ranges for ROTEM parameters in children are age-dependent and were evaluated recently [27]. The most striking finding in that study was that children aged 0–3 months exhibited accelerated coagulation and strong clot firmness, despite showing prolonged standard plasma coagulation test results. Similar to adults, also in children fibrinogen concentrations, platelet count and FXIII contribute to clot firmness as measured with ROTEM assays. In addition, it was demonstrated that children aged 4–24 months showed the lowest 2.5% percentiles for clot strength, indicating low reserve when exposed to hemodilution and blood loss.

Administration of fresh frozen plasma was recommended for treatment of dilution coagulopathy and in massive transfusion scenarios [41–46]. Remarkably, there is not a single randomized controlled trial published proving the beneficial use of FFP for treatment of perioperative bleeding in children with respect to improved clinical outcome. One of the rarely published randomized controlled trials using prophylactic FFP administration in preterm babies to prevent or reduce periventricular hemorrhage failed to provide evidence for routine early use of FFP [47]. Observations of a pilot study in 30 children revealed that the use of FFP for intraoperative volume replacement had led to significantly higher fibrinogen levels (184.4 ± 9.2 mg/dl) as compared to colloid fluid resuscitation using albumin (106.4 ± 7.6 mg/dl) [48]. However, there was no difference in terms of mean amounts of intraoperative or postoperative blood loss and transfusion requirements.

A meta-analysis by Stanworth et al. [47] revealed no significant improvement if FFP was used for treatment of coagulopathic bleeding. The British guideline stated a grade A recommendation to avoid the use of FFP as a simple volume replacement [49]. Recommended dosages of 10–15 ml/kg FFP may not be adequate to achieve a clinically meaningful improvement in hemostatic potential [50–52], but higher doses were often be limited by the considerable necessary volume load.

Fibrinogen was specified to be the first clotting factor to fall to critically low levels during life-threatening hemorrhage in adults and children. Intraoperative substitution with human fibrinogen concentrate was effectively used to treat fibrinogen deficiency in a case report series in pediatric craniofacial surgery [21], by a prospective randomized trial in adult patients undergoing aortic valve/ascending aorta replacement [53], during adult radical cystectomy [54], in a clinical trial on adult major orthopedic surgery [35], and in a case report series in patients with massive hemorrhage [55–57]. Fibrinogen concentrate offers a very good safety profile [58, 59], but clinical evidence for recommendation of minimal tolerable fibrinogen levels by good-quality trials is still lacking. Recent European guidelines [45, 46] recommend higher fibrinogen cut-off levels (150–200 mg/dl) as compared to international guidelines [60].

There is growing evidence that acquired FXIII deficiency is frequent in the surgical and acute care setting [61]. A study of neurosurgical patients showed that postoperative fibrinogen levels of 150 mg/dl together with a marginal decrease of FXIII (<60%) was associated with a 12-fold increase in relevant bleeding (need for transfusion and/or surgical revision) [62]. Results from a prospective randomized trial in adults [63] and other clinical investigations [62, 64, 65] underline the potential need for maintaining adequate FXIII levels (above 50–60%) during perioperative bleeding situations, but need further investigations.

Data from off-label treatment of recombinant activated factor VII (rFVIIa) was published from neurosurgical procedures in children [66, 67]. Results from a prospective randomized trial in pediatric cardiac surgery did not show significant differences in blood loss after administration of 40 μg/kg rFVIIa as compared to placebo [68]. Likewise, two prospective randomized trials from blunt or penetrating injuries in adults failed to reduce transfusion of RBCs after administration of rFVIIa as compared to placebo [69]. Thus, administration of rFVIIa for treatment of severe bleeding may only be efficacious if critical amounts of fibrinogen and platelets were established or if extremely high doses of rFVIIa were administered [70].

Antifibrinolytic agents have shown to significantly decrease blood loss and reduce allogeneic blood transfusion in pediatric cardiac and scoliosis surgery [71, 72]. Similar beneficial effects of tranexamic acid were also observed in a double-blind randomized trial in pediatric craniosynostosis surgery [73]. However, optimum doses are unknown, and reported dosing ranges from 10 to 100 mg/kg loading doses and 1–10 mg/kg/h infusion rates.

Conclusion

Development of dilutional coagulopathy during major surgery is an important clinical problem. There is a pivotal need for fast and reliable coagulation testing that guides through (mostly multifactorially caused) coagulopathic bleeding. This might effectively be managed by using a viscoelastic point-of-care device (ROTEM or thrombelastography). Acquired fibrinogen deficiency is a common finding and should be treated with substitution of fibrinogen concentrate, whereby minimal plasma fibrinogen levels need to be defined by further well-controlled studies. Substitution with other coagulation factors (e.g. FXIII levels < 60%) should be based on laboratory findings. FFP transfusion in a dose of 30 ml/kg might be useful for treatment of severe hemorrhage as adjunctive to basic treatment with coagulation factors but should only be considered after exclusion of any other factor that might influence hemostasis (i.e. fibrinogen deficiency, hyperfibrinolysis, acidosis, hypothermia, low platelet count/impaired platelet function). Based on current literature, routine use of rFVIIa was not supported. Perioperative treatment with antifibrinolytic agents might be helpful in reducing the amount of bleeding and reducing transfusion requirements in noncardiac pediatric surgery with a high risk of bleeding. Further well-controlled studies are urgently needed to determine the effect of a targeted, laboratory-based coagulation management for treatment of pediatric dilutional coagulopathy.

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