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Review

Pediatric perioperative bleeding – Basic considerations☆

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ABSTRACT

Massive perioperative bleeding following major surgery or trauma is one of the main causes of preventable morbidity and mortality in the pediatric patient. Non-surgical or coagulopathic bleeding may be caused by a congenital or acquired coagulation disorder that was undetected prior to surgery, by disorders in the coagulation cascade resulting from specific surgical interventions such as liver transplantation or cardiopulmonary bypass to repair congenital heart diseases or when massive blood losses develop as in children with severe multiple trauma, major surgery, craniosynostosis and scoliosis. Hence, their management requires adequate preoperative evaluation to identify the children at high risk of bleeding and thus be always prepared for massive intraoperative bleeding, in addition to perform early interventions to prevent the multiple complications of coagulopathy in hemorrhagic shock, such as hypothermia, acidosis and hemodilution.

Sangrado perioperatorio en niños. Aspectos básicos

Palabras clave:
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RESUMEN

El sangrado perioperatorio masivo secundario a una cirugía mayor o trauma es una de las principales causas de morbimortalidad prevenible en el paciente pediátrico. El sangrado no quirúrgico o coagulopatico puede ser producido por un transtorno de la coagulación congénito o adquirido no detectado antes de la cirugía, disturbios en la cascada de la coagulación producidos en ciertos procedimientos quirúrgicos específicos como en transplante hepático o en el Bypass Cardiopulmonar durante la corrección de cardiopatías congénitas o cuando se presentan pérdidas sanguíneas masivas como ocurre en niños con politrauma severo, cirugía mayor, craniosinostosis y escoliosis. Por lo tanto su manejo requiere una adecuada evaluación preoperatoria para identificar los niños con alto riesgo de sangrado y de esta

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manera estar siempre preparados para un sangrado intraoperatorio masivo, adicionalmente realizar intervenciones tempranas para evitar los múltiples aspectos de la coagulopatia en shock hemorrágico como la hipotermia, la acidosis y la hemodilución.

Methodology

A literature review was undertaken on pediatric perioperative bleeding based on Pubmed, Medline, Ovid and Cochrane data.

Introduction

Bleeding caused by trauma or major surgery that requires massive transfusion is one of the main causes of preventable morbidity and mortality in the adult patient. Pediatric patients are no the exception. The Pediatric Perioperative Cardiac Arrest study (POCA) reported that one of the principal causes of death in pediatric patients during the trans-operative period is cardiovascular in origin, caused by hypovolemia secondary to blood losses. Its management requires adequate evaluation and the right therapeutic approach.[1,2]

The two most important causes of perioperative bleeding are failure to control blood vessel bleeding at the surgical site, or surgery performed in highly vascularized tissues that are left unsutured or are difficult to cauterize, as is the case in scoliosis surgery or craniosynostosis correction. A meticulous surgical technique and proper patient selection contribute to reduce the risk of bleeding. The second cause is non-surgical or hemostatic bleeding that presents as generalized bleeding at venipuncture sites, through the nasogastric tube, through the surgical wound margins and the presence of hematuria. Its etiology may be due to:

1. A pre-existing un-diagnosed coagulation disorder prior to surgery (Hemophilia, Von Willebrand disease).
2. Co-existence of established underlying pathologies such as chronic renal disease, liver disease, malignancies (Wilms tumor) and the use of drugs.
3. Alteration of hemostasis related to the surgical procedure as in the case of cardiopulmonary bypass or liver transplantation.
4. Massive blood losses in major surgery or trauma.[3]

The objectives of pediatric perioperative bleeding management include:

1. Identification of patients at risk of bleeding (preventive).
2. Understanding any surgery-related hemostatic changes.
3. Adequate replacement of blood losses.
4. Prevention and early treatment of complications from massive transfusion.
5. Establishment of pharmacological therapies to control excessive perioperative bleeding.
6. Consider the usefulness and limitations of the various coagulation tests.
7. Trying to reduce the number of transfusions through blood preservation programs, whenever possible.[4–6]

Aspects concerning the development of hemostasis

For several years the understanding and characterization of the pediatric and adult hemostatic system were considered alike. Today we know that maternal coagulation factors do not cross the placental barrier.[7]

The levels of coagulation factors measured at birth are the result of the fetal synthesis that starts around the fifth week of gestation; fetal blood may coagulate around week 11 of gestation.

All coagulation factors and its inhibitors are qualitatively normal at birth and differ from those of the adults only in terms of quantity. At birth, the plasma levels of vitamin K-dependent factors (II, VII, IX, and X) and contact factors (XI, XII, prekalikrein, and high molecular weight kininogen) are decreased by around 50% as compared to adult values and only after the sixth month of life reach 80% of the adult values. This results in a slight prolongation of PPT, PT, INR in lab tests up to the 3rd to 6th months of age. Factor VIII and the Von Willebrand factor remain elevated during the first months of life as compared to adult values.

The plasma levels of coagulation inhibitors, Antithrombin III (ATIII), Protein C and Protein S, tissue factor pathway inhibitor (TFPI) are reduced between 15% and 50% of the adult values and this continues up to the 3rd to 6th month of life. Protein C concentration and TFPI continue to be low until adolescence.

An in vitro platelet function decrease has been described due to a decline in the response to a series of agonists including epinephrine, ADP, collagen and thrombin, which result in reduced in vitro platelet aggregation tests. However the decrease in the platelet activity has not yet been elucidated because thromboelastography studies show shorter coagulation times explained by higher levels of Von Willebrand factor and hematocrit that contribute to platelet adhesion in the vascular injury lesion.

Fibrinogen values are similar in neonates and adults; however, some evidence suggests that neonatal fibrinogen is qualitatively dysfunctional and remains in its fetal form until the first year of life; biochemical studies have shown that neonatal fibrinogen has different electric charges and increased phosphorus content as compared to adult fibrinogen.

Plasminogen also exhibits quantitative and qualitative differences in children and is 50% of the adult values during the first six months of life when it reaches normal levels. Additionally, the plasminogen inhibition factor (PIF), a primary inhibitor of fibrinolysis exhibits normal to increased values

in the neonatal stage. These differences lead to decreased plasmin generation and a depressed fibrinolytic activity in neonates.[8–11]

In conclusion, the hemostatic system in children exhibits considerable differences as compared to adults; however, despite these quantitative and qualitative differences in all coagulation components, neonates and children have excellent hemostasis and it has been proven that except for heart surgery, neonates and children under six months of age do not present excessive bleeding during surgery.[12]

Current management of pediatric perioperative bleeding

Identify patients at risk for bleeding

The clinical history and the physical examination are critical in the preoperative period to identify any coagulation disorders in children.[13,14]

Coagulation tests may be normal and thus a high rate of suspicion in patients at risk for bleeding is crucial. The relevant points that alert the anesthesiologist are a history of previous surgical or dental procedures bleeding, positive family history of coagulation disorders and easy bleeding.[15] The type of surgery is also a determinant factor. Patients undergoing surgery with low risk of bleeding and with a negative history do not require coagulation tests prior to the procedure. Those undergoing surgeries with a high risk of bleeding should always have coagulation tests, PT, PPT and platelets. If the pre-anesthesia evaluation suggest a history of bleeding, the patient shall be referred to the hematologist for analysis before surgery and be prepared during the procedure according to the coagulation disorder diagnosed. The two most important variables to order a lab test are the child's clinical record and the surgical procedure proposed. If there is a history of any personal or family coagulation disorders, coagulation tests shall be performed.[16–19]

The patients requiring more in depth analysis are children with a clinic suggestive of coagulation disorders, altered coagulation tests in pre-surgical examinations or a positive family history.

An incidental finding of a prolonged PPT may be frequent in pediatric patients without a clinical history of bleeding. It is usually secondary to the presence of a lupus-like anticoagulant triggered by transient viral infection-related antibodies. Despite an extended PPT it is not associated to bleeding. Mixing the patient's plasma with control plasma and then measuring the PPT confirms the presence of lupus-like anticoagulant. If the PPT is corrected there it is a coagulation deficit, otherwise it is a lupus-like anticoagulant.[20,21]

Severe clotting disorders such as hemophilia A or B show up in the first year of life; however, mild coagulation disorders may occur at times of stress such as surgical trauma. The most frequent congenital coagulation disorders in pediatric patients are Von Willebrand's disease (VWB), hemophilia A, hemophilia B and platelet function disorders. Acquired bleeding disorders may be the result of Vitamin K deficiency that should be suspected in children with malabsorption syndrome, extra hepatic bile duct atresia or in new born babies that failed to receive Vitamin K at birth, in children with certain diseases such as chronic renal failure, chronic hepatic diseases, and cyanotic congenital heart disease.[22]

Acquired Von Willebrand disease has been reported in children with left-to-right shunt congenital heart disease, children with Wilms tumor, lymphoproliferative disease, autoimmune disease, hypothyroidism and in children using medications such as valproic acid.[23–26]

Hemostatic changes in the perioperative period

Perioperative bleeding is a pendulum that oscillates towards bleeding during surgery and towards coagulation in the postoperative period. Depending on the type of procedure the coagulation system is affected in various ways, which leads to various management strategies.[27,28]

Specific surgical procedures

Heart surgery

Bleeding of the pediatric patient during heart surgery is one of the main causes of morbidity and mortality. Cardiopulmonary bypass-associated coagulopathy and hence, perioperative bleeding is more severe in neonates and infants than in adults.

The factors involved in hemostatic failure are hemodilution produced by a discrepancy between the baby's blood volume and the primed bypass circuit volume, by the activation of contact factors with the bypass circuit and by the initiation of a systemic inflammatory response with activation of the clotting and fibrinolysis system, resulting in consumptive coagulopathy and reduced platelet activity.

There is an increased risk of perioperative bleeding in children under one year of age, less than 8 kg of weight, cyanotic congenital heart disease, complex cardiac pathologies, prolonged surgical time, high level of complexity of the surgical procedure and re-intervention.[29,30]

Liver transplant

Usually children who require liver transplantation exhibit typical disarrangements of end-stage liver disease with decreased coagulation factors, thrombocytopenia and increased fibrinolytic activity. Intraoperatively clotting disorders occur, particularly during reperfusion whenever there is a massive release of the plasminogen tissue activator factor resulting in massive fibrinolysis.

Factors associated with high risk of bleeding are portal vein hypoplasia, using a reduced liver graft, children with severe pre-transplantation liver disease, children with acute liver failure, children under two years old and re-transplantation.[31–33]

Scoliosis

Blood losses are due to a large bloody surface of muscle and bone tissue, particularly in children with neuromuscular scoliosis apparently related to a dysfunction of the vascular phase, increased coagulation factors consumption and increased fibrinolysis. Furthermore, these are patients with

altered nutritional status and use of anticonvulsant medication that disrupts the coagulation cascade.[34–37]

Craniosynostosis

The difficulty in the trans-operative management of these patients lies in the management of massive blood losses because of their young age, since most children under 6 months old have limited blood loss tolerance.

In the study by Meyer et al., it has been estimated that during surgery the child loses 91 plus or minus 66% of the blood volume. Blood losses vary according to the type of correction (25% loss in sagittal suture, 21% unicoronal, 65% bicoronal, 42% in metopic) and the surgical technique used.

Blood losses are the result of scalp dissection where 30% of the blood volume may be lost, elevation of the vascular periosteum, osteotomies and eventual damage of a venous sinus where bleeding is usually massive and catastrophic.

Different studies report that the use of blood transfusion in craniosynostosis surgery is practically unavoidable. Risk factors for increased perioperative bleeding are the child's age, the number of sutures involved and the surgical procedure to be performed.[38–41]

Trauma

Trauma is a universal public health problem. It is the first cause of death in people over one year of age around the world.

In the past it was believed that coagulopathy was a late phenomenon, secondary to acidosis, hemodilution and hypothermia – the so-called lethal triad. It is currently recognized that the cause of coagulopathy is multifactorial and that it is an early primary phenomenon caused by the activation of the thrombomoduline and protein C system resulting in systemic anticoagulation, in addition to increased fibrinolytic activity.

The risk factors for increased bleeding are the level of severity of the trauma, the length of time between the trauma itself and initial treatment care, chest trauma, presence of shock, level of acidosis, and hypothermia at admission.[42–45]

Massive blood losses

Massive blood loss is defined as the loss of one blood volume in 24 h, 50% loss of one blood volume in 3 h, losses over 1.5 ml/kg/min for 20 min or a transfusion of over 40 ml/kg of red cells. Major blood losses should be acknowledged early and the shock and its consequences such as coagulopathy must be treated promptly. Trauma and massive transfusion are associated with coagulopathy secondary to tissue trauma, hypoperfusion, dilution and coagulation factors and platelets consumption. Damage control resuscitation or hemostatic resuscitation, aims at achieving early control of the coagulopathy.[46–49]

Dilution of coagulation factors and platelets are an important cause of coagulopathy in massively transfused patients. Hemodilution induces interstitial edema, disruption of microcirculation and oxygenation, resulting in acidosis. Hydroxyethyl Starch (HES) causes the outflow of blood proteins into the interstitial space, reduces FVIII plasma concentration and Von Willebrand's factor, decreases the platelet function and inhibits the Factor XIII – fibrin polymers interaction. Low molecular weight solutions and the latest generation solutions, cause less disruptions in the hemostatic system.[50]

Hypothermia is associated with the risk of uncontrollable bleeding and death in massively transfused patients. Hypothermia induced coagulopathy is attributed to platelet dysfunction, reduced coagulation factors activity and induction of fibrinolysis. Hypothermia induces platelet morphological changes and disrupts activation, adhesion and aggregation. The enzyme cascade for coagulation factors is efficient if the temperature is above 35 °C; there is a 10% decrease in the coagulation factors activity per every one-degree of temperature decrease. The effect of hypothermia on in vivo coagulation is usually underestimated because the evaluations of the conventional coagulation tests are done at 37 °C.[51]

In massively transfused patients, hypoperfusion and NaCL overdosing during resuscitation often induce acidosis. Acidosis alters coagulation through various pathways: platelets change their structure and shape and become spherical and deprived of their pseudopodes at a pH below 7.4. Factor VII bonding to tissue factor is decreased, the coagulation factors activity diminishes and results in lower thrombin generation that is the main cause for coagulopathic bleeding. Moreover, acidosis leads to increased fibrin degradation further worsening the coagulopathy.

Anemia contributes to coagulopathy because the red blood cells (RBC) induce the marginalization of platelets by enabling their binding to the endothelium. Moreover, the RBCs modulate the biochemical and functional responses within the activated platelets. They support the generation of thrombin through the exposure of membrane pro-coagulating phospholipids; stimulate the release of alpha granules and the platelet production of cyclooxygenase.[52,53]

Conclusions

Optimal massive bleeding management in major surgery or trauma in pediatric patients requires a comprehensive knowledge of their hemostatic system and of the disruptions in the coagulation system during the specific surgical procedure. Early intervention is a must to avoid any coagulopathy-triggering factors such as hypothermia, acidosis and hemodilution.

Adequate blood loss replacement is essential to reduce morbidity and mortality in the pediatric surgical patient. Readiness is of the essence in situations where massive bleeding is expected.

The article "Management of perioperative bleeding in children. Step by step review"[54] will analize the main considerations of transfusion therapy, the prevention and management of massive transfusion complications and the use of perioperative hemostatic agents.

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Conflicts of interests

The author has no conflicts of interest to declare.

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