Prevention and Management of Apheresis Complications

14

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14.1 Introduction

The majority of apheresis procedures performed for both therapeutic and collection purpose are completed without complications. However, both expected and unexpected side effects can occur anytime. Furthermore, various factors may increase the risk of adverse events during apheresis therapy. These examples include, but are not limited to, environment, staff, and type of apheresis procedure, replacement fluids, anticoagulation, and the comorbidities of the donor or the patient. Furthermore, adverse events can occur during or after apheresis procedure and may not specifically be related to the apheresis procedure itself (e.g., hematomas or infection from access). However, all adverse events must be appropriately treated and documented to prevent future events. Thus, anticipation of potential adverse events and, therefore, earlier recognition and possibilities to diminish the severity need a thorough understanding by the apheresis practitioner. In this chapter, many variations of side effects that can occur during an apheresis procedure are discussed.

14.2 An Overview of Types and Severity of Complications

The complications can be of immunologic (e.g., hemolytic or anaphylactic transfusion reactions and reaction to ethylene oxide) or non-immunologic (hematomas, bleeding complications, and vasovagal reactions) origins. Side effects can also be

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categorized as systemic and/or local and acute or delayed as some side effects may occur many days after the therapeutic apheresis procedure. The severity of adverse events is typically categorized as mild, moderate, or severe. Mild and moderate reactions are much more common than severe reactions. Mild reactions are usually limited to mild paresthesia, pallor, weakness, intermittent dizziness, sweating, nausea, and/or an episode of vomiting, transient hypotension, light-headedness, hyperventilation, and asymptomatic bradycardia. Moderate reactions may be defined as mild reaction with symptoms that do not respond to routine nursing interventions (per standard operating procedure [SOP]) and require clinician at the bedside and might require termination, either briefly or permanently, of apheresis procedure. Severe reactions require immediate termination of procedure. Severe reactions may be characterized by long-lasting unconsciousness, convulsions, tetany due to severe hypocalcemia, incontinence, and, in rare occasions, death. Surveillance and acknowledgment of such side effects require well-trained apheresis staff, nursing, and clinicians.

14.2.1 Reactions of Immunologic Origin

14.2.1.1 Etiology, Identification, and Prevention

The majority of immunologic reactions seen by the apheresis practitioner are transfusion reactions secondary to the use of blood components during the procedure, as either a priming or replacement fluid. Transfusion reactions can be seen after transfusion of all blood components and can be acute (occurring within 24 h of transfusion), delayed (within 3–14 days), or late (after many years, such as transfusion-transmitted viral infection). Typically, institutional transfusion protocols shall be followed with at least vital signs recorded at regular intervals to monitor for reactions. The frequency of such monitoring depends on the type of procedure performed, the patient's hemodynamic condition and comorbidities, and institutional policies.

Based on the international hemovigilance reports, hemolytic transfusion reaction can be caused by human errors. Around 1 in 13,000 blood component units is transfused to the wrong patient (not always with adverse consequences), and up to 1 in 1300 pre-transfusion blood samples is taken from the wrong patient (http://www.transfusionguidelines.org.uk/transfusion-handbook/5-adverse-effects-of-transfusion n.d.). The error can be made by the health-care staff collecting the tubes for laboratory testing (misidentification of the patient, mislabeling on tubes), in the laboratory or immediately prior to the transfusion (misidentification of the patient to be transfused). When in apheresis procedures blood components are used for replacement fluid all good nursing practices associated with blood administration must be performed. All individuals involved need to be alert. All blood handling (labeling, sampling) needs to be checked carefully based on institutional policy to prevent clerical errors that may lead to adverse event(s). In addition to clerical errors, the majority of transfusion reactions are related to acute hemolysis, sepsis due to bacterial contamination of blood products, transfusion-associated

circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). Less common but more severe are allergic reactions, posttransfusion purpura, and transfusion-associated graft-versus-host disease (Ta-GvHD).

When a patient develops new signs and symptoms during or after the administration of a blood component, a transfusion reaction should be suspected, and blood administration shall be stopped immediately. All suspected transfusion reactions, including those during an apheresis procedure, should be reported to the hospital transfusion service, and it is advised also to report to a regional and/or national hemovigilance system depending on the regulations. Posttransfusion blood samples need to be drawn from the patient for laboratory tests used to investigate the cause of the observed transfusion reaction, especially to rule out hemolytic transfusion reaction. It is also advisable to notify the physician covering the transfusion service.

14.2.1.2 Immune-Mediated Hemolytic Transfusion Reaction: Early Versus Delayed Reaction

The most severe and feared immune-mediated hemolytic transfusion reaction is an intravascular destruction of red blood cells (i.e., hemolysis), which can be either acute or delayed and can lead to mortality or significant morbidity. Acute reactions are usually caused by IgM antibodies present in the patient's plasma directed against the ABO-incompatible or IgG antibodies directed against other red blood cell antigen-incompatible donor erythrocytes. Less commonly, the acute hemolysis is caused by antibodies present in transfused donor plasma directed against the patient's RBCs. This intravascular hemolysis may normally occur during or immediately after the transfusion and may be seen during therapeutic apheresis procedures. Other causes of hemolysis include thermal effects (storage and/or heating during administration by incorrectly working blood warmers), infusion of hypotonic or hypertonic solutions with a blood product, or rarely by contamination by microorganisms.

During intravascular hemolysis, the RBCs lyse, and hemoglobin is released into the circulation. Free hemoglobin protein is bound to haptoglobin and removed from circulation by the reticuloendothelial system. Massive intravascular hemolysis may overwhelm hemoglobin clearance mechanisms leading to accumulation of excess of free hemoglobin. The circulating free hemoglobin may result in acute kidney injury resulting from direct proximal tubular cell toxicity through generation of radical oxygen species, cast formation and subsequent tubular obstruction, and vasoconstriction resulting from free hemoglobin scavenging of nitric oxide. Symptoms associated with intravascular hemolysis include fever, chills, hypotension (can lead to shock), tachycardia, back pain, headache, nausea, and hemoglobinuria and can lead to disseminated intravascular coagulation (DIC) and multi-organ failure causing mortality. Treatment includes immediate discontinuation of the transfusion, fluid administration, and catecholamine support with continuous vital monitoring. Laboratory evaluation in these cases should include a direct antiglobulin test (DAT), repeated compatibility testing (e.g., crossmatching donor units with pre- and post-transfusion blood from the patient), complete blood count, lactate dehydrogenase

(LDH), bilirubin, haptoglobin levels, and an urine analysis for the presence of hemoglobinuria.

Delayed hemolytic transfusion reactions are frequently unnoticed but may occur 1–4 weeks after transfusion and usually appear as extravascular hemolysis. In extravascular hemolysis, red blood cells are phagocytized by macrophages in the spleen and liver and are therefore less clinically significant. Delayed reactions result from either development of a new red blood cell antibody (IgG) or the anamnestic response of a preformed antibody following antigen re-exposure through transfusion. The majority of patients with delayed hemolytic reactions only require close monitoring of the hemoglobin, however, anamnestic response due to anti-Kidd antibody may cause intravascular hemolysis.

14.2.1.3 Transfusion-Related Acute Lung Injury (TRALI)

Another acute complication after transfusion is TRALI. TRALI is usually caused by donor antibodies to the patient's human leukocyte antigens (HLA) and/or human neutrophilic antigens (HNA). These antibodies result in activation of the patient's neutrophils, which damage pulmonary endothelium and lead to pulmonary edema. According to the international consensus (Kleinman et al. 2004), a diagnosis of TRALI requires new acute lung injury occurring within 6 h of transfusion, evidenced by hypoxia and bilateral pulmonary infiltrates on the chest X-ray, as well as the absence of preexisting acute lung injury or other risk factors for pulmonary edema. Treatment for TRALI is supportive with the symptoms usually resolving within 48–96 h from onset. It's often difficult to distinguish TRALI from transfusion-associated circulatory overload (TACO) which is also a frequent complication seen during or after transfusion. The patients with TACO are usually hypertensive and have tachycardia. Treatment of TACO is diuresis and/or slowing the infusion rate (or possibly terminating the transfusion and the therapeutic apheresis procedure), while in TRALI, diuresis is contraindicated.

14.2.1.4 Transfusion-Associated Graft-Versus-Host Disease (Ta-GvHD)

A severe delayed complication of transfusion of cellular blood components in immunocompromised patients is the Ta-GvHD. Ta-GvHD arises when transfused alloreactive T lymphocytes (in the graft) attack the patient's cells (the host). Since the patient is immunosuppressed, the patient's immune systems fail to eliminate the transfused T-cells. Instead, the surviving donor's T-cells attack recipient cells that have mismatched HLA antigens. Ta-GvHD can be seen in patients with congenital or acquired immunodeficiency and patients who undergo intensive chemotherapy or transplantation (need for immunosuppressive drugs) and receive blood components with viable T lymphocytes. Symptoms will start usually 1–2 weeks after the transfusion. Target organs are the skin, intestine, liver, and bone marrow. Characteristics for the Ta-GvHD are fever, skin rash, and diarrhea. Laboratory tests reveal signs of bone marrow failure (pancytopenia due to donor's T-cell alloreactivity) and liver malfunction. Ta-GvHD is associated with high mortality rate since there is no effective treatment.

As leukocyte-reduced cellular components contain sufficient T-cells to cause Ta-GvHD, leukocyte reduction of the blood components is not an optimal strategy to prevent such complication. Only irradiation of cellular blood products can prevent Ta-GvHD. Following irradiation of cellular blood components with at least 25 Gy, the T-cells in these blood components are no longer able to divide and, therefore, unable to cause Ta-GvHD. Hence, established guidelines for irradiation of blood products in these patients shall be followed. In case of peripheral blood $CD34^+$ cell donation, all persons (donating autologous or allogeneic $CD34^+$ cells) in need of transfusion of cellular blood components should solely receive irradiated blood components from a period of 3 months before donation until end of donation. Also when the apheresis machine needs to be primed with blood in case of pediatric or small-size donors, irradiated blood must be used.

14.2.1.5 Other Immunologic Reactions

If plasma-containing blood products are transfused during apheresis, allergic and anaphylactic reactions are also potential complications caused by plasma proteins. Symptoms of a mild allergic transfusion reaction include vasodilatation, edema, and erythema. Additional symptoms can include pruritus, urticaria, and headache. Localized allergic reactions may be treated with antihistamines and/or steroids and, if necessary, a short interruption of the procedure. Rarely, allergic reactions during an apheresis procedure can be caused by ethylene oxide (ETO), a gas used for the sterilization of the disposable. Symptoms of an anaphylactic reaction include dyspnea, wheezing, severe hypotension, bronchospasm, bronchospasm, and shock. The specific allergen causing the anaphylaxis is often unknown, but these patients should be worked up for IgA deficiency and IgA antibodies, and it may be worthwhile gathering other history in regard to allergies from the patient. It is also important to obtain the history of medication that the patient may take prior to or during the procedure since the reaction may be related to the medication and not the procedure itself. Treatment of an anaphylactic reaction includes immediate discontinuation of the procedure and immediate aggressive resuscitation support. Significant allergic reactions may warrant premedication with antihistamines and/or steroids prior to future apheresis procedures, but this may be nowadays routine in procedures with blood component infusion in many centers. In case of significant allergic reactions in donor apheresis procedures, it is advised to refrain from donation.

14.2.2 Reactions of Non-immunologic Origin

14.2.2.1 Bacterial Infections and Sepsis

Blood components can be contaminated from many sources. In developed countries, traditional transfusion-transmitted infections as human immunodeficiency virus (HIV) and the hepatitis viruses are extremely rare. On the contrary, bacterial infections are rather common and can lead to severe morbidity and mortality. Bacterial contaminations of blood components are most often derived from the collection line especially if the skin decontamination prior to venipuncture is not done

properly. The normal skin flora, such as the coagulase-negative staphylococci, rarely produces severe infections, although febrile reactions may occur. Different pathogenic bacteria can be derived from an asymptomatic infection present in the donor during donation. Some of them may lead to life-threatening reactions. Other sources of bacteria include incorrect sterilization of the collection bags and contamination during the preparation of the blood components. Transfusion-related sepsis is more common with platelet transfusions than with other blood products because of their storage temperature at 20–24 °C. However, red blood cell unit can also be contaminated with bacteria, such as gram-negative ones. Symptoms include rapid onset of fever, rigors, abdominal cramping, and hypotension (even septic shock) and may be indistinguishable for many causes of immunologic reactions described above. Disseminated intravascular coagulopathy (DIC) can also occur. It is important to immediately stop the apheresis procedure to limit the amount of possibly contaminated blood. The needle should be kept intravenously and open with saline in the likely event that medications may need to be rapidly administered. Fluid resuscitation is also useful to treat hypotension and stimulate urine production. Further treatment includes supportive care, including intravenous fluids, as well as administration of appropriate antimicrobial agents. It is important to note that similar "transfusion bacterial contamination type" reactions can be observed if the infected central venous line (mostly in patients if the line is already inserted for a long time) is used. Therefore, it is important to culture both the patient (before antibiotics is given) and the blood product, when available, if transfusion-related sepsis is suspected. Usually the organisms grew must be identical between the infected unit and the patient's blood in order to confirm bacterial contamination from the transfused unit.

14.2.2.2 Reactions Related to Volume Shifts During Apheresis

Volume shifts normally occur during any apheresis procedure. It is critical to consider the patient's total blood volume, the extracorporeal blood volume during the apheresis procedure, and the hemodynamic changes during the procedure. For example, it is important to ensure that the extracorporeal volume (ECV) and red cell volume is within the 15% of the patient's total blood volume and total red cell volume during the procedure, respectively. If the volume removed is more than 15% of the patient's blood volume, then crystalloid or colloid fluids shall be given to avoid hypotension. It should be noted that in certain patients (older age, vasoactive medication, sepsis), the compensatory mechanisms may be less effective, and in pediatric apheresis where the disposable is primed with blood components prior to the procedure, no rinse back should be performed after the procedure to avoid extra fluid being given.

Hypotension during an apheresis procedure may be associated with a vasovagal reaction, citrate toxicity, anaphylaxis, or hypovolemia secondary to volume loss. Contemporary apheresis machines are designed to use less extracorporeal volume (ECV) than earlier versions, which helps to minimize the risk of a hypovolemic side effect. However, especially in small children, the ECV of the apheresis circuit can be relatively high.

Hypotension due to hypovolemia is characterized by a hypotension with tachycardia and tachypnea. In contrast, vasovagal reactions, which are also associated with hypotension, are characterized by concurrent bradycardia. In patients of low total blood volume (TBV) (low body weight or pediatric patient), it may be necessary to prime the extracorporeal circuit with 5% albumin or RBCs to avoid adverse events. To treat hypotension due to intravascular volume depletion, the procedure is usually paused temporarily, and the patient is given a fluid bolus and assessed by the supervising physician.

At the end of the apheresis procedure, the apheresis operator must calculate the patient's net fluid balance. Fluid delivery varies depending on the apheresis device utilized and the type of procedure performed. Volume lost secondary to vomiting, diarrhea, and perspiration should also be taken into account. The net difference between these total "remove" and "replace" volumes should be calculated, documented, and communicated to the clinical service to include in tracking of the patient's fluid intake and output.

14.2.3 Hypotension During Apheresis While on ACE Inhibitors

Hypotension during apheresis procedures can also be seen in individuals taking angiotensin-converting enzyme (ACE) inhibitors 48–72 h prior to the procedure. These medications are used primarily for the treatment of hypertension by inhibiting the vasoconstriction. Besides that, ACE inhibitors also decrease the ability to inactivate bradykinin. Bradykinin triggers an increased vascular permeability and dilatation of the blood vessels resulting in decreasing the blood pressure. Release of bradykinin is caused by the activation of the kinin system, and activation of this system can be initiated by apheresis due to contact with negatively charged plastic disposable kits or the LDL apheresis column, as well as activation of pre-kallikrein-activating factor which is present in albumin. Hypotensive reactions, bradycardia, flushing, and dyspnea have been reported in patients receiving blood products and therapeutic plasma exchanges (TPE). Since apheresis is an elective procedure, ACE inhibitor should be held approximately 24 h prior to the procedure. Angiotensin receptor blockers are acceptable alternative to ACE inhibitors during the treatment period. If the procedure is emergent and the patient has taken an ACE within 24 h, plasma may be used as a replacement fluid to avoid the potential refractory hypotension caused by this medication.

14.2.4 Vasovagal Reaction During Apheresis

A vasovagal reaction is a reflex of the parasympathetic nervous system (vagal nerve), usually following activation of the sympathetic nervous system which can be triggered by anxiety, pain (from line placement) associated with the procedure, hypocalcemia during the procedure (discussed below), or hypovolemia from volume shift as described above. Overcompensation of the parasympathetic response

leads to cardioinhibitory response, characterized by negative chronotropic and inotropic effects leading to a decrease in cardiac output. Such phenomena may cause hypotension and sometimes syncope. Concomitantly, the overcompensation of the parasympathetic nervous system leads to vasodilatation resulting in marked hypotension (blood pressure can be as low as 50/20 mmHg) without reflex tachycardia. This should be distinguished from the tachycardia usually associated with hypovolemia. In addition to changes in vital signs, clinical symptoms of a vasovagal reaction include pallor, diaphoresis, nausea and vomiting, syncope, and possibly convulsions. Sometimes there is incontinence of urine and/or feces. The situation can be very similar to epileptic seizures.

Nursing interventions shall start when observing a pale person starting to yawn during apheresis with attempting to calm the donor/patient with deep breathing exercises, coughing, laughing, or repositioning to reduce pain and increase comfort which may be sufficient to treat a vasovagal reaction. If necessary, these reactions can also be treated by stopping (in donors) or temporarily pausing the procedure (in patients), placing the donor/patient in the Trendelenburg position, and providing a fluid bolus.

14.2.5 Anticoagulation in Apheresis with Citrate and Heparin

14.2.5.1 Citrate

Citrate is being used very frequently in routine life, especially in the food industry as flavoring and buffering agent in drinks and food. Citrate is also used as anticoagulant in medical procedures. Its use as anticoagulant in the transfusion medicine has been since 1913. Citrate works through chelation of divalent cations such as calcium and magnesium. By binding the ionized calcium, various steps within the coagulation system are inhibited, and thus, clotting can be avoided in the extracorporeal circuit. During apheresis, in continuous-flow procedures, citrate is reinfused continuously, while in intermittent flow devices, citrate is returned intermittently. Consequently, this citrate infusion during apheresis may result in decreased serum levels of ionized calcium and magnesium. Ionized calcium levels can decrease 25% or more during apheresis procedure. The decrease of ionized calcium will lead to an increased production of parathyroid hormone (PTH), aiming to increase ionized calcium level (Buchta et al. 2003). Within 15 minutes after the start of the procedure, PTH levels are elevated.

Besides being an essential cofactor in the coagulation cascade, calcium also plays an important role in the conduction of nerve impulses and in the contraction of muscles. Because of a decrease in ionized calcium, an increased excitability of neurons to the point of spontaneous depolarization can be achieved and, thus, is responsible for some of the symptoms of hypocalcemia.

14.2.5.2 Citrate Toxicity: Citrate-Induced Hypocalcemia

Symptoms of hypocalcemia can be separated into minor, moderate, and severe (see Table 14.1) (Lee and Arepally 2012). With minor reactions, the donor or patient

Table 14.1 Citrate-induced hypocalcemia

Severity	Clinical presentation
Mild	Acral and/or perioral paraesthesia Flushing Shivering Headaches Sneezing Light-headedness
Moderate	Nausea and vomiting Abdominal pain Nervousness Irritability Tremor Muscle spasms Involuntary muscle contractions Tetany Drop in blood pressure
Severe	Cardiac arrhythmia Seizures

may experience a metallic taste, as well as perioral and/or acral paraesthesia. With moderate reactions, the symptoms remain, despite nursing interventions such as slowing down the whole blood flow rate, increasing the anticoagulant to whole blood ratio (AC/WB ratio) if possible, and/or administering calcium supplementation. The donor or patient may suffer from nausea, vomiting, abdominal pain, shivering, light-headedness, tremors, and hypotension mimicking hypovolemia and vasovagal reactions. With severe reactions, symptoms may progress to carpopedal spasm, tetany seizure, and cardiac arrhythmia, specifically prolonging the QT interval. Special attention is needed for patients under sedation or in coma and for pediatric patients, who may not be able to verbally alert the apheresis staff of citrate toxicity symptoms.

Patients receiving blood components as replacement fluid or with a preexisting baseline hypocalcemia prior to apheresis procedure may be at greater risk of citrate-related complications. Similarly, patients with severe liver or kidney disease are also at higher risk of citrate toxicity due to their inability to adequately metabolize citrate. A periodic check of ionized calcium levels and prophylactic calcium supplementation may be warranted in these patients.

14.2.5.3 Citrate Toxicity: Citrate-Induced Metabolic Acidosis and Subsequent Hypokalemia

Various other cofactors should also be mentioned as an effect of citrate infusion during an apheresis procedure. Alkalosis will decrease the ionized calcium levels and therefore increase the effects of citrate. It should be noted that bicarbonate is produced during citrate metabolism, increasing the pH in the blood. In patients with reduced renal bicarbonate excretion, such as those with renal failure or on diuretic medication, bicarbonate accumulation influences the pH considerably. These patients may require monitoring of their acid-base status, especially since metabolic

alkalosis increases the potassium intake into the cells, leading to hypokalemia, possibly also leading to cardiac arrhythmias. Besides the additional bicarbonate production, hyperventilation can also cause alkalosis.

14.2.5.4 Citrate Toxicity: Citrate-Induced Hypomagnesemia

Besides the chelation of calcium, ionized magnesium is also bound to citrate. Significant drops in magnesium levels during apheresis procedures are measured. For example, during a plateletapheresis procedure, a decrease of 30% of the magnesium level is demonstrated. The decrease of magnesium is also more pronounced, and it recovers more slowly than calcium. Magnesium influences the electrical activity of myocardial cells because of changes in the stabilization of the axons and the release of neurotransmitters needed to activate the muscles. The symptoms of hypomagnesaemia are rather similar to the effects of hypocalcemia. As calcium and magnesium both bind to proteins, especially albumin (competitive inhibition), in case of hypocalcemia, more magnesium will be bound, leading to hypomagnesaemia. If citrate toxicity is suspected and calcium supplementation does not resolve symptoms, hypomagnesemia and magnesium supplementation should be considered.

14.2.5.5 Prevention and Management of Citrate Toxicity and Use of Heparin as an Alternative Anticoagulation

If citrate toxicity is suspected, the apheresis operator or nurse may elect to slow the flow rate, adjust the citrate infusion ratio if possible, or temporarily pause the procedure. Modern apheresis devices often will not allow infusion rates of citrate that exceed 1.2 mL/min/L blood volume in order to prevent citrate toxicity and hypocalcemia. Some apheresis devices will reduce the whole blood flow rate automatically in order to maintain the citrate infusion rate even lower. Oral (calcium carbonate) and intravenous (calcium chloride or calcium gluconate) calcium supplementation are additional treatment options. In therapeutic apheresis procedures, especially in patients with low baseline ionized calcium levels or procedures where a high amount of citrate will be needed (large volume of stem cell collection), prophylactic calcium administration should be considered. If significant citrate toxicity persists, use of an alternative anticoagulant, such as heparin, or a mixture of heparin and citrate may be used. However, it should be noted that heparin is also associated with adverse events, such as bleeding secondary to persistence in patient plasma several hours after the apheresis therapy and association with heparin-induced thrombocytopenia (HIT). Therefore, it is best to use heparin-only anticoagulation in individuals with citrate allergy and/or in patients with severe renal and hepatic dysfunction.

14.3 Hypothermia

In apheresis techniques, whole blood is separated in the apheresis machine. The desired blood component is collected, and the remaining blood components are returned to the donor or patient. By measuring the temperature of the circulating

blood, the hypothalamus can keep up to the mark of the body temperature. When the blood temperature decreases, e.g., because of cooling down of the blood to be returned from the apheresis machine, or reinfusion of colder fluids, the hypothalamus will react by sending impulses to the skin resulting in chills leading to a discomfort in the donor/patient. To avoid cooling down during the apheresis procedure, the use of blood warmers needs to be considered.

14.3.1 Local Adverse Events

None of the apheresis procedures can be performed without venous access, in the form of either peripheral or a central venous catheter. A few apheresis procedures can be performed using single needle access, however, the majority of procedures require double needle access with an acceptable drawn and return flow. For donor procedures, the cubital fossa is usually used for access, however, there is a relatively complex anatomy there. The vein, artery, and nerve are next to each other. Anatomic variances can be the cause that in some persons frequently arterial punctures are performed instead of venous. In such case, an adequate pressure after removing the needle is needed to avoid large hematomas.

When peripheral access is used, phlebotomy may be associated with bruising, hematoma, nerve injury, infections, phlebitis, and/or deep venous thrombosis. Bueno et al. (2006) studied almost 5200 apheresis procedures in 1373 donors and found that in 3.3% of the procedures, hematomas were seen, related to the experience of the operator (<500 procedures performed, more hematomas), prior donations with apheresis machines (experienced donors, more hematomas), and the vein where the venipuncture was made. The basilic vein showed a higher rate of hematoma than cephalic and median veins and others due to various causes such as anatomy and elasticity. Surprisingly, low diastolic blood pressure was also correlated to more hematomas. A clear explanation for this isn't possible. There were no correlations with age, previous hematomas, and gender.

Another problem is nerve injury caused by the needle. The donor or patient will observe a burning shooting electrical pain during the time that the needle is in place. In some cases, the pain starts hours after the venipuncture. In a study from Horowitz (2000), 24 patients with causalgia after venipuncture were analyzed. In a follow-up of 1.5–3 years, only three improved spontaneously, six showed no change, and 15 worsened. However, in a study published by Newman and Waxman (1996), 52 of 56 individuals showed full recovery, and four had mild residual complaints. In the study from Horowitz, however, 70% of the persons involved had also a hematoma worsening the pressure on the nerve.

Risks associated with central venous catheters include infection, thrombosis, hemorrhage, air embolism, pneumothorax, hematothorax, and/or arrhythmias. Even in very experienced clinicians, the puncture to insert a subclavian catheter is complicated by a pneumothorax in 1.5–3% of the patients. Thus, before connecting an apheresis device to a central venous line, the position of the line has to be assured by adequate means (e.g., X-ray). In all procedures, the apheresis operator must

regularly evaluate the site of venous access, checking for signs of hematoma, infection, thrombosis, bleeding, and correct insertion.

14.4 Medication Adverse Events

Donors for peripheral hematopoietic progenitor cell collections need to be mobilized prior to the apheresis procedure with medication as G-CSF and/or plerixafor. This medication has its own series of side effects (discussed in Chapts. 5 and 6). Some of these side effects can be difficult to differentiate between the medications and apheresis procedure. Examples are not only gastrointestinal disorders as nausea and vomiting but also headaches, musculoskeletal pains, and fatigue. These can be caused by mobilization and medication and yet, at the same time, can be a side effect from the apheresis procedure, for instance, citrate intoxication.

14.5 Prevention of Apheresis Complications in Children

Indications for performing apheresis procedures in adults also apply to children. However, children are not little adults, so special considerations are required. Children undergo complex development of physiology, psychology, cognition, and behavior. For example, there are few opportunities for an adequate venous access (small vessels), the relatively small TBV in combination with the ECV of the apheresis device and the collected volume and increased sensitivity to hypocalcemia. Also, pediatric patients may also have difficulty in concentration and have increased mobility, and these factors can affect the success of an apheresis procedure.

Depending on the specific apheresis procedure, the ECV can be as high as about 300 mL. This ECV is unacceptable in (very) young children. In adolescents and adults without significant comorbidities, an extracorporeal volume of 15% is well tolerated. In very small children or hemodynamically unstable patients, the maximum tolerable ECV may be lower, such as 10%. If the expected ECV is not acceptable, a blood or albumin prime of the apheresis disposable may be needed. With this, isovolemia can be maintained throughout the procedure.

Because of the small peripheral veins in (very) young children, they may be not large enough to maintain the blood flow rates needed for apheresis. The adequacy of vascular access will vary according to the age, gender, and size of the child. Normally, a 16–17-gauge needle is needed for the drawn line and a 19–22-gauge needle for the return line. A double-lumen central venous catheter can be preferred in younger children with its own risks and considerations as discussed above. Sedation may also be needed for central line placement or in conjunction with muscular paralysis in a patient on mechanical ventilation. The effect of sedatives and other medication administered before apheresis may wear off during a procedure, perhaps partly as a result of drug removal. Thus, for patients requiring sedation during apheresis, repeated dosing during the procedure may be needed.

In children, the burden of the anticoagulant, such as citrate, used in the apheresis procedure is relatively large. For example, relatively more citrate per kilogram of body weight per minute is administrated, and together with the limited metabolic capacity of the pediatric liver and/or kidney, there is an increased risk of hypocalcemia. Symptoms of hypocalcemia and hypomagnesemia in children are difficult to recognize. They may be subtle and difficult to assess, especially in young or sedated children. In children, clinical manifestations of citrate toxicity can consist of acute abdominal pain (with or without vomiting), agitation, pallor, and sweating, followed by tachycardia and hypotension. Hypotension in very sick or unconscious children during apheresis should be assumed to be due to citrate toxicity and treated appropriately.

Toxic effects of citrate anticoagulation can be avoided in children by carefully monitoring the ionized serum calcium levels pre-, during, and post procedure and providing calcium supplementation if necessary. In adolescents and older children, minor symptoms of hypocalcemia can be treated with oral calcium supplementation. Calcium can also be administered intravenously; in many apheresis centers, intravenous calcium supplementation is given routinely.

In colder conditions, humans lose heat via the head and the trunk. The body shape of a child differs from that of an adult. The head and trunk can be over 60% of the total body length. Therefore, smaller children can lose greater heat. This is something an apheresis physician must think of, especially when also colder fluids are returned as is the situation during apheresis procedures. Therefore, the room temperature needs to be high, and the use of blood warmers needs to be considered.

14.6 Expert Point of View

Apheresis procedures are generally safe, and serious adverse events occur very rarely. However, we must learn from each other's adverse events in an attempt to avoid it as much as possible. Since side effects occur only rarely, registration at least in regional but preferably in global registries (e.g., apheresis registration of the World Apheresis Association) of all procedures and their side effects is of high importance. With all gathered data, the frequency, the probable cause of specific side effects, and their management options can be evaluated. These lessons can make apheresis safer in the future.

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