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Review

Pediatric red cell and platelet transfusions

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ABSTRACT

The aim of pediatric transfusions should be based on the concept of avoiding unnecessary transfusions without jeopardizing the patient safety and providing correct blood components when there are well founded indications to transfuse. Despite considerable efforts from transfusion services to increase transfusion safety, transfusions are still associated with preventable and unpreventable adverse effects that may, in the worst case, have severe and fatal consequences. Transfusions to pediatric patients constitute a small proportion of all transfusions but have higher incidence of adverse events compared to adults. Pediatric transfusions consist of intrauterine transfusions, top-up transfusions to neonates and young children, exchange transfusions in the management of hemolytic disease of newborn (HDN), in addition to sickle cell crisis, chronic transfusion therapy in thalassemia patients, massive transfusion in trauma, HLA- and HPA-compatible platelets in immunized patients and neonates with fetal neonatal alloimmune thrombocytopenia (FNAIT). Packed red cells (PRCs) and platelet (PLT) concentrates are the most utilized blood components and will be reviewed here.

1. Introduction

Finding the balance between preventing unnecessary transfusions and hindering delays in life-saving transfusions is the real state-of-the art of transfusion medicine. Expected benefits of transfusions should always be more than the risks. Transfusion support is essential not only in life-time transfusion-dependent pediatric patients with chronic diseases like hemoglobinopathies, but also in patients who need a single/few units that may be necessary or life-saving, like in surgery with blood loss patients´ own reserves cannot compensate for. Transfusion services work continuously to improve the quality of red cell and the platelet concentrates. However, vigilance for transfusion complications is indispensable, despite the fact that transfusions have never been safer than today.

This article will focus on PRC and PLT transfusions in pediatric patients. The objective is mainly indications for intrauterine and red cell exchange transfusions in newborns and older children, PLT transfusions in FNAIT, in addition to both PRC and PLT transfusions in pediatric hemato-oncology, trauma and surgery patients. An overview of our institutional practice will be given for each topic. Risks of transfusions will be briefly discussed. Patient blood management in pediatric patients is a relatively untouched ground and further reflections and continual development and research are more than ever warranted, especially regarding indications, thresholds and monitoring the effect of transfusions.

2. Red cell transfusion

Indication for PRC transfusions is anemia resulting in decreased tissue oxygenation due to production failure, immunologic destruction of red cells or blood loss. Intensity of the clinical symptoms depends on how acute the anemia occurred and whether there is ongoing bleeding. Anemia due to RBC production failure is mainly because of malignant bone marrow disease, non-malignant diseases like aplastic anemia and chronic diseases like kidney disease, rheumatoid arthritis, in addition to therapy-related anemia. Transfusion thresholds vary among institutions and guidelines; either restrictive; 70 g/L being usually the transfusion trigger or liberal strategy with 100 g/L being the transfusion trigger in adult patients with hematological malignancies and such a practice is also adopted to pediatric patients [1]. In stable, critically ill children a hemoglobin threshold of 70 g/L was used instead of 95 g/L without increasing adverse outcomes [2]. Since the study group did not include premature infants or children with severe hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease, the findings do not apply to these patients.

2.1. Intrauterine transfusions

Intrauterine transfusion is indicated when clinically significant blood group alloantibody(ies) of a pregnant women lead to severe fetal anemia, so-called hemolytic disease of the fetus (HDF). The most

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frequent antibody involved is anti-D, thereafter anti-K [3,4]. Blood group O RhD negative PRCs also antigen negative for the actual antibody(ies) are used. Being an invasive procedure intrauterine transfusion can boost the antibody production and worsen the anemia. Intrauterine blood transfusion may also be indicated in fetal anemia because of parvovirus B19 infection in the mother [5].

2.2. Red cell exchange transfusions in newborns

The main indication for red cell exchange in newborns is HDN [3,4]. HDN is the same condition as HDF, which is due to the mother´s clinically significant blood group antibody(ies) directed to an antigen/antigens the baby has inherited from the father. Besides being negative for the actual antigen(s) PRCs to be used to prepare exchange transfusion blood, should be ABO compatible both with the mother and the newborn. The same applies to plasma regarding ABO blood group compatibility. In most of the cases O RhD negative, K negative, five or less than five days old PRCs and thawed AB plasma is put together to reconstitute the exchange transfusion blood, following volume reduction by centrifuging PRCs and replacing SAGMAN solution with AB plasma. In Norway the only plasma in use is Octaplasma® that is virus inactivated and batch-produced. There are no reports of TRALI with transfusion of Octaplas® in the Norwegian hemovigilance system. Premature newborns, especially those under 1500 g and babies who have received intrauterine transfusions should receive irradiated PRCs to prevent transfusion-associated graft versus host disease; therefore the units should be irradiated before reconstitution.

2.3. PRCs for hemato-oncology patients

Transfusion-dependency may be life-long in pediatric patients with hemoglobinopathies or can define a patient who needs transfusions in a limited period of time e.g. leukemia patients undergoing allogeneic hematopoietic stem cell transplantation (AHSCT). Among the other supportive measures, transfusion support has made AHSCT possible; a treatment otherwise could be fatal due to bleeding or severe anemia in aplasia. How much phenotype-matched the PRC transfusions should be is an ongoing debate. The risk of alloimmunization (see also below) to foreign red cell antigens is always present since full phenotype-matched transfusion with all the 352 known RBC antigens is impossible unless autologous blood is used. Luckily not all red cell antibodies are clinically significant [6]. However, antibodies against high frequency antigens may be challenging to investigate immunohematologically, because it might be difficult to exclude underlying clinically significant antibodies. Further serologic investigation with specially selected antigen negative cells supplemented by genomic RBC typing at reference laboratories may then be needed. The standard prerequisite for all PRC transfusions is ABO and RhD match. In addition K negative blood is provided to K negative women in childbearing age in Norway and the rest of Europe, but not in USA and Canada [7,8] where transfusion with K positive blood is the major cause of alloimmunization. Although additional phenotype match is not required, in our practice, for long-time transfusion-dependent pediatric and especially sickle cell and patients, extended phenotyping for C, c, E, e, Jka, Jkb, Fya, Fyb, S and s or genomic RBC typing is performed. PRC units as much phenotype-matched as possible are then chosen for transfusion; priority is in the same order as listed above.

2.4. Exchange transfusions in older children

Exchange transfusion is indicated in sickle cell crisis, acute chest syndrome or cerebral malaria [9,10]. Besides ABO, RhD and K compatibility, UK guidelines advocate additionally C, c, E, e as a minimum and less than 7 days old units [4]. According to our institutional guidelines we also choose, to the extent there are available blood donors, additionally Jka, Jkb, Fya, Fyb, S and s compatible PRC units to prevent alloimmunization. The units should preferably be less than 10 days old but we prioritize phenotype-match and let up to 14 days old units. For a Fya negative Fyb negative patient, Fya compatibility is generally provided based on blood donor accessibility.

2.5. Choosing ABO-type of blood components for patients who receive ABO incompatible (AHSCT)

PRCs, platelet concentrates and plasma have to be ABO compatible both with the patient and the donor [11]. When blood group O PLT concentrates are chosen to an ABO incompatible patient the PLTs must be of low titer anti-A and/or anti-B for that antigen in order not to risk hemolysis [11].

2.6. Pediatric trauma patients, patients requiring surgery

Acute massive blood loss and trauma-induced coagulopathy can cause death in pediatric patients [12]. Immediate surgical management of the bleeding focus together with balanced PRC, plasma and PLT transfusions is needed until circulatory stability is achieved [13]. Keeping the patient warm and using less crystalloid solutions are essential. Tranexamic acid and fibrinogen concentrate are also part of several protocols. Many trauma centers have standard multi-transfusion protocols for adult patients; in our practice a trauma/multi-transfusion package is composed of five units of PRCs, five units of Octaplasma and one unit of PLT concentrate either apheresis or buffy coat consisting of five donors. However, the optimal composition of blood components for pediatric patients is not defined yet.

As preparation for an elective surgery, hemoglobin control to detect eventual anemia and investigate the etiology of it and in case of iron-deficiency iron replacement would reduce peri-operative blood transfusion requirements.

2.7. Cytomegalovirus (CMV)

In Norway universal leukoreduction of all cellular blood components have been in use since 2001 and leukoreduced PRCs and PLT concentrates are considered as CMV negative. Some other countries have prerequisite for not only leukoreduction but also blood components from CMV seronegative donors for very low-birth-weight infants, premature, infants undergoing transplantation [4,14].

2.8. How fresh the PRCs should be for pediatric patients?

It is demanding to provide enough amounts of fresh PRC units in the blood bank inventory at all times. Definition of what is old is debatable: ≤5 days, ≤7 days or ≤14 days? However, deleterious effect of older PRC transfusions in pediatric patients and especially hyperkalemia can be avoided by using ≤5 days-old RBCs for premature [4,13]. Our institutional guidelines recommend ≤5 days-old RBCs not only the premature, but also for term newborns and older children (< age 16). However, due to donor availability for patients with thalassemia and sickle cell disease, the limit may be extended to 10 and sometimes up to 14 days.

3. Platelet transfusions

In our practice apheresis and buffy coat PLTs are considered as equivalent also for pediatric transfusions. Infection epidemiology in Norway does not imply a more stringent strategy. The concern for increased donor exposure through whole blood-derived (WBD) platelets from four to five donors has not proved to be justified. However, some institutions use only apheresis PLTs for pediatric patients [4]. Nahirniak and co-authors strongly recommend, though with a moderate level of evidence, that leukoreduced WBD PLTs produced by buffy coat or PLT-rich plasma methods should be used interchangeably with apheresis