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Review

Red cell transfusion in paediatric patients with thalassaemia and sickle cell disease: Current status, challenges and perspectives

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ABSTRACT

Notwithstanding the high safety level of the currently available blood for transfusion and the decreasing frequency of transfusion-related complications, administration of labile blood products to paediatric patients still poses unique challenges and considerations. The incidence of thalassaemia and sickle cell disease in the paediatric population may be high enough under specific racial and geographical contexts. Red cell transfusion is the cornerstone of β-thalassaemia treatment and one of the most effective ways to prevent or correct specific acute and chronic complications of sickle cell disease. However, this life-saving strategy comes with its own complications, such as additional iron overload, alloimmunization and haemolytic reactions, among others. In paediatrics, the dependency of the transfusion outcome upon disease and other recipient characteristics is more prominent compared with the adults, owing to differences in developmental maturity and physiology that render them more susceptible to common risks, exacerbate the host response to transfused cells, and modify the type or the clinical severity of the transfusion-related morbidity. The adverse branch of red cell transfusion is likely the overall effect of several factors acting synergistically to shape the clinical phenotype of this therapy, including inherent donor/blood unit variables, like antigenicity, red cell deformability and extracellular vesicles, as well as recipient variables, such as history of alloimmunization and inflammation level at time of transfusion. This review focuses on paediatric patients with β-thalassaemia and sickle cell disease as a recipient group with distinct transfusion-related characteristics, and introduces new concepts for consideration, not adequately studied and elucidated so far.

1. Introduction

The most common monogenic diseases on a global scale include hereditary disorders of haemoglobin (Hb), mainly thalassaemia and sickle cell disease (SCD). The sickle mutation is allocated on the *HBB* gene (Glu6Val, βS) and results in the intracellular polymerization of the deoxygenated Hb molecule, the pathophysiological hallmark of all clinical forms of SCD. Pathological Hb polymers potentially damage the red blood cell (RBC) membrane forming abnormal rigid sickle-shaped cells. These malformed cells can cause vaso-occlusion (VOC) leading to distal tissue ischaemia and inflammation [1] that underlie acute painful sickle-cell crisis. The chronic haemolysis with acute exacerbations, and the progressive vasculopathy, oxidative stress and organ dysfunction, which start in infancy and continue throughout life, result in increased morbidity and premature death [2]. The commonest and most severe form of SCD is the homozygous HbSS which is also referred as sickle cell anaemia (SCA). Other forms of SCD include compound heterozygous conditions, such as cases of HbS mutation co-inherited either with β-thalassaemia mutations (HbS/β°-thalassaemia or HbS/β^{+}-thalassaemia), or HbC mutation (HbSC) and HbS with other beta-globin variants such as HbSD or HbSOArab [3].

The clinical forms of thalassaemia disorders are caused by mutations affecting the α and/or β peptide chains of Hb. The clinical presentation depends on the resulted imbalance in the α/β-globin chain ratio and the subsequent chronic haemolytic anaemia, ineffective erythropoiesis, compensatory increased gastrointestinal iron absorption

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and medullary expansion outside the bone marrow. During the last decade, a trend for classification of the various thalassaemia syndromes has been established that is largely based on clinical and management criteria, rather than on molecular characteristics. Currently available treatment for both thalassaemia and SCD includes blood transfusions applied either regularly or sporadically according to the clinical presentation of the diseases, starting from infancy (28 days-1 year) or childhood (< 18 years). Thalassaemia patients are nowadays categorized as having transfusion-dependent (TDT) or non-transfusion-dependent thalassaemia (NTDT) [4]. TDT patients are not able to synthesize enough Hb to survive, unless regular RBC transfusions are given. NTDT patients also need transfusions, but only sporadically or at regular intervals for a certain period of time. TDT mainly includes patients with β-thalassaemia major (βTM) and severe forms of HbE/β-thalassaemia, whereas NTDT includes β-thalassaemia intermedia, HbH disease and some types of HbE/β-thalassaemia [4]. It should be noted that the clinical criteria used for the classification of thalassaemia patients can change over time based on both progression of the disease and advances in its clinical management. Consequently, the TDT/NTDT classification does not reflect a lifelong classification, but only the current clinical status of a patient that may change [4,5].

Paediatric patients have the longest potential lifespan which makes appropriate transfusion policy and safety of paramount importance in this population. Newborns (< 28 days of life), infants and young children are small sized, immature and particularly vulnerable in specific transfusion complications. Transfusing infants and children, therefore, does not only imply smaller transfusion volumes. There are unique challenges, considerations and host responses to transfused blood, resulting, among other, by a range of physiological differences compared with the adults, including higher average Hb concentration and oxygen requirements. Moreover, children at different ages also vary not only in blood volume, but also in metabolic rate and body surface area to mass ratio. These disparities lead to specific transfusion indications and doses. Specialized components and additional safety measures are applied for transfusion to different paediatric patient groups and for different clinical indications, including thalassaemia and SCD.

2. RBC transfusion for the treatment of Thalassaemia in paediatrics

Transfusion therapy is the cornerstone of the optimal management of thalassaemia. By providing normal allogenic RBCs, ineffective erythropoiesis is suppressed along with most of the subsequent catastrophic pathophysiological mechanisms of the disease [6]. However, the chronic transfusions introduce secondary complications, mainly related to alloimmunization and iron overload/toxicity (see below), which contribute to high morbidity rate [4]. Nowadays, implemented improvements in transfusion practices and iron–chelation therapies have decreased the incidence and severity of co-morbidities, increasing substantially the life expectancy of thalassaemia patients [7–9].

The initiation of transfusion therapy in a child with thalassaemia remains a delicate and critical decision made by haematologists and other specialists, after the overall clinical evaluation of the patient. Despite the fact that the genotype can provide some initial indication about the expected clinical severity of the disease and the likelihood of developing TDT, the decision is made at clinical level. As the borderline between thalassaemia intermedia and major is sometimes blurred, it is not always possible to predict the evolution of the disease to TDT or NTDT. Hb level by itself is not enough to drive the critical decision to start a regular transfusion program, and thus, additional criteria are taken into consideration, including whether the child is thriving or not, the height velocity, weight gain and spleen size. Mistreated children over-transfused to the point of iron toxicity, which would probably have been better without regular transfusion at all, may hopefully belong to the past, but should guide us towards future decision making.

In clear cases of thalassaemia major, the presence of persisting anaemia (with Hb < 7 g/dL at least on two occasions in a 2-week interval), along with clinical manifestations that include fatigue, poor feeding, developmental delay or regression, growth deceleration, and symptoms or signs of cardiac dysfunction determine the initiation of regular transfusion therapy. Coexistence of anaemia-contributing factors, such as iron deficiency, infection or glucose-6-phosphate dehydrogenase (G6PD) deficiency, are also taken into consideration. In TDT patients, regular RBC transfusions start from infancy or early childhood, usually before the age of three. Despite evidence that late initiation of regular transfusions in those cases increases the risk of RBC alloimmunization, providing low risk RBC units in alloimmunized patients remains a challenge, especially in the developing countries [9,10].

In children with NTDT (often intermedia), however, transfusions are usually given in adulthood to manage or prevent some of the complications of the disease and only sporadically during childhood, in order to treat acute anaemia resulted by a transient factor, such as viral infection or surgical intervention [9]. Then, the child who can maintain (at steady state) Hb at satisfactory concentration is reevaluated. In cases of fall in height velocity or peak bone mass, regular transfusions are given until *epiphyseal plate closure*. Re-evaluation of the possibility to gradually withdrawn regular transfusions is then carried out, given that many patients can adapt to chronic anaemia without substantial bone marrow stress [11]. Nevertheless, it is worth mentioning that according to several observational studies, regularly transfused NTDT children, especially with β-thalassaemia intermedia, have better growth variables, while the development of morbidities (such as hypercoagulability, silent strokes, pulmonary hypertension and extramedullary hematopoietic masses) in regularly transfused NTDT adults seems to be lower [4,5,11–14]

In chronic transfused patients, maintaining Hb levels above 9–10.5 g/dL is sufficient to both inhibit bone marrow expansion and minimize transfusion-related iron overload [6,15]. In patients with cardiovascular disease and/or excessive extramedullary haematopoiesis, transfusion thresholds of 11–12 g/dL have been reported to be beneficial. Regarding transfusion intervals, they usually range from 2 to 4 weeks according to the severity of anaemia and the clinical response to therapy, along with personal decisions of the patient and socioeconomic conditions, including access to hospital and blood supply. The volume of RBCs transfused into children is calculated by using a formula that incorporates the patients' weight, the desirable and the actual Hb levels [16].

3. RBC transfusion for the treatment of Sickle Cell Disease in paediatrics

Blood transfusions, either simple, exchange, or chronic, in SCD remain one of the most effective treatments for both acute and chronic complications. The transfusion of allogenic RBCs in these patients corrects anaemia and, at the same time, dilutes out the number of sickle cells that underlie VOC and vascular damage [17]. The most common goal for HbS concentration is less than 30%, a threshold that is based mainly on expert consensus rather than randomized trials [18]. It is worth mentioning that although children are more able to tolerate large increases in Hb than adults [17], the most effective way to achieve this HbS threshold is by exchange transfusion, which removes sickle cells without the risk of hyperviscosity [19]. Thus, simple RBC transfusions as well as exchange transfusions are given acutely in severe clinical events to offer immediate improvements in blood flow and tissue oxygenation, among other. Chronic transfusions are usually given monthly to prevent several long-term complications, such as strokes, in both children and adults. Apart from replacing the non-deformable sickle RBCs with normal ones, the chronic transfusions further suppress their long-term formation [3]. According to the Cooperative Study of Sickle Cell Disease's infant cohort, 35% of the enrolled children with HbSS disease received at least one blood transfusion by the age of five [20]. Moreover, it has been estimated that nearly half of the paediatric SCD