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Review

Blood derived products in pediatrics: New laboratory tools for optimizing potency assignment and reducing side effects

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ABSTRACT

Neonates and children can develop rare bleeding disorders due to congenital/acquired coagulation Factor deficiencies, or allo-immune/autoimmune complications, or can undergo surgeries at high haemorrhagic risk. They then need specialized transfusion of blood components/products, or purified blood extracted products or recombinant proteins. Blood-derived therapies conventionally used for management of affected infants with genetic/acquired deficiencies, bleeding problems (coagulation Factor reduced or missing) or thrombotic disorders (reduced or missing anticoagulant proteins) pose some additional risks. These remedial therapies can cause tolerance when used very early in life and, sometimes needed, repeatedly. The introduction of recombinant proteins has allowed manufacturers to produce large amounts of the proteins usually present at very low concentration in blood. This has also changed the risk pattern of plasma-extracted products, especially in terms of continual reduction of viral transmission. Many efforts have been made over these past decades to reduce the risks associated with the use of all these products in terms of viral and bacterial safety, as well as immune disorders but they are not the objective of this article.

Other associated side effects are the presence of undesired activities in blood products, which can produce thrombotic events or adverse reactions. The progressive introduction of blood derived products has greatly improved the prognosis and quality of life of affected patients. This concerns whole blood, but also blood cell concentrates, mainly platelets and red blood cells, plasma, while the blood extracted products are increasingly replaced by recombinant proteins. All these therapeutic products, i.e. blood extracted drugs, improve health and quality of life for hemophiliac's A or B, or patients with auto/allo-immune thrombocytopenias or with rare bleeding disorders, and those with thrombotic events occurring in childhood, which are mainly due to Protein C or Protein S deficiencies (congenital or acquired). Progress in analytical methods and biotechnology allow better control of the manufacturing processes for all blood derived or plasma extracted products and recombinant proteins, and contribute to improved manufacturing processes to minimize the occurrence of side effects. These adverse events can be due to the aging of the blood cell concentrate with release of their granule content, and generation of EVs, which can produce anaphylactic reactions and risk of thrombosis, but also to the presence of activated coagulation Factors in purified products, such as Factor Xia as recently identified in immunoglobulin concentrates. Characterization and measurement of contaminant products is of special usefulness during product preparation and for optimization of manufacturing processes for purified extracted products, but also for recombinant proteins. The pharmaceutical industry introduces these new methods for validating manufacturing processes, or for quality control assessments. The objective is first to warrant the full quality and safety of the lots produced, and assure the highest efficacy with the lowest risks when used in patients. For cell concentrates and fresh blood, storage conditions are critical and measurement of analytes such as EVs or Annexin V allows evaluation of quality of each individual transfused pouch. In addition to all the rules around viral and bacterial transmission risk, and immune tolerance, our available laboratory methods contribute to reducing the side effects of blood cell concentrates and derived plasma products, as well as those of the therapeutic recombinant proteins.

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Contents

1. Introduction

Blood derived products, as well as recombinant proteins, or those modified to enhance their activity or in vivo half-life, are used in pediatrics for many applications: treating congenital or acquired bleeding tendencies; thrombotic complications (such as fulminans purpura with homozygous or severe Protein C deficiency) and high haemorrhagic risk surgery [1–7]. While security for transmission of infectious agents, or immune compliance are well controlled, new risk Factors have been identified for trace amounts of contaminants or the presence of activated coagulation Factors, which can expose treated patients to the risk of thrombosis [8–10]. New laboratory methods are very useful for monitoring manufacturing processes and the quality of released products [11–13]. In addition, new products are highly purified and a high potency can be reached with low volumes of injected material, as it is the case for both Factors VIII and IX [14–17]. Assay methods and reliable reference material is an absolute requirement for an accurate assignment of drug potency [11–13,18,19]. New techniques and the available laboratory tools will be discussed in this report. They are useful for the evaluation and the prevention of risks and side effects due to the presence of "non-desired activities" (such as contaminants, activated Factors and released products due to the cell storage lesion for cell concentrates) [20–23]. The viral and immunological safety will not be addressed in this report, as well-established and standardized procedures are available for offering the lowest risk Factors [1–4,6,7].

Use of blood products in pediatrics involves many different situations [24–32]. The best known disorder is hemophilia, due to a deficiency of Factor VIII for hemophilia A, or a deficiency of Factor IX for hemophilia B [33–35]. But other rare disorders have been reported and can involve all proteins of the coagulation cascade, particularly Factor V, Factor VII, Factor X, Factor XI, Factor XII and Factor XIII, which are all associated with less or more severe bleeding events; clinical manifestations occur for different cut-off thresholds of the Factor concentrates [34,35]. Delayed bleeding has been identified in children with Factor XIII deficiency, congenital or sometimes acquired due to development of autoantibodies or to intoxication. Acquired Factor II deficiency has been reported in association with some childhood infectious diseases. These hemorrhagic episodes can be life threatening and need immediate reversal to manage affected patients [25,27,28,30].

Other bleeding risks can result from anti-platelet alloimmunization or auto-immunization [32]. Thrombocytopenia must be rapidly identified in affected newborns and infants and should be controlled and treated with platelet concentrates (the quality of which is of essence to avoid side effects and anaphylactic reactions). The other clinical circumstances requiring procoagulant therapies concern extensive surgery associated with a high bleeding risk or grafts. In this context, a significant amount of transfused blood products (fresh/frozen plasma, whole blood, or blood cell concentrates) is needed [27,29,30]. Conversely, recurrent thrombosis, stroke or fulminans purpura can affect other infants. This complication is mainly due to congenital deficiencies of the anticoagulant Protein C or Protein S, which can be homozygous in some cases, or to acquired (hopefully frequently transitory) Protein S auto-antibodies (following varicella/chicken pox infections) [36–42]. Infusion of purified blood extracted or recombinant products is necessary for managing patients, sometimes associated with corticotherapy [38,41]. Protein deficiencies or the presence of variants with a decreased activity have been reported [36,37,39,41,42]. These patients, who may develop severe clinical pro-thrombotic complications can be successfully treated with Protein C, or Protein S concentrates, or a combination of both [38]. Acquired Protein S deficiencies have been reported in children with varicella/chicken pox. The deficiency is due to development of anti-Protein S antibodies, and occurrence of thrombosis at various sites (peripheral or venous) is frequent [39]. Substitution with Protein S preparations is not useful as the presence of the antibodies can make it inefficient, and these patients are treated with heparin. Fortunately, these antibodies are transitory, and disappear within a few months.

Lastly, in some cases, activated preparations such as prothrombin complex concentrate (Autoplex, FEIBA, etc.), or activated purified Factors (activated recombinant FVIIa) can be used to reverse severe or life threatening bleeding episodes, or when patients are unresponsive to usual therapies (as, for example hemophiliacs with auto-antibodies to FVIII or to FIX, or in liver surgeries/grafts during the anhepatic phase [8,10]. Although very rare in children, activated Factors or FVIIa can also be used to reverse the bleeding risk induced by direct oral anticoagulants (DOACs), especially before an urgent surgery.

The challenge remains to supply the missing anticoagulant Factors without contamination with other proteins or with activated Factors. This article focuses on the safety and reduction of side effects induced by transfused or injected blood derived products or recombinant proteins, and the laboratory tools which improve the specific analytical control at the various steps of product preparation: in process manufacturing; quality control of lots; and individual testing of some products before therapeutic us, such as platelet concentrates. Infectious and immune safety of these products has benefited from major progress over these 3 past decades (since the discovery of HIV infection, and other blood transmitted viruses such as hepatitis B antigen or hepatitis C), and is not discussed in this report. Our objective is to show how advances in laboratory methods for blood coagulation proteins, their activated forms and cell released extracellular vesicles