International Society of Blood Transfusion (ISBT) Working Party (WP) on Global Blood Safety (GBS)

Recommendations

on local production of virus-inactivated cryoprecipitate

Rationale for use of locally produced, virus-inactivated cryoprecipitate

According to the WHO Global Database on Blood Safety, in low and medium development index countries cryoprecipitate is in current use to treat patients with bleeding disorders, particularly hemophilia A. As it is prepared in its "native" (non-virus-inactivated) form, cryoprecipitate carries considerable risks of exposure to transfusion transmissible infections. However, the major viral risks of HIV, hepatitis B and hepatitis C can virtually be eliminated through virus inactivation of plasma or cryoprecipitate itself employing available pathogen reduction technologies.

Therefore, the ISBT WP on GBS wish to emphasize the importance of preparation of cryoprecipitate, virus inactivated (called hereafter: "Cryo-VI") by established pathogen reduction/virus inactivation technologies, in resource limited settings where commercial clotting factor concentrates (CFC) are unavailable or unaffordable. Such use would dramatically increase the clinical safety of locally-produced cryo-VI , but also promote availability and accessibility of an effective therapeutic product, not only for patients with hemophilia A, but also those with von Willebrand Disease and fibrinogen depletion/dysfunction.

In resource limited settings of low and medium HDI (Human Development Index) countries an adequate supply of quality and safe blood products (labile blood components as well as stable plasma-derived medicinal products) is often unreliable, unaffordable, insufficient or absent. As a result, many patients in need of these blood products go untreated. Additionally, due to an inadequate infrastructure in donor screening and donation testing, as well as regulation, treated patients receiving local blood products may be exposed to high risks of transmission of blood-borne infectious agents.

Drugs of choice for treatment of hemophilia A and most forms of von Willebrand Disease are commercial CFC, which are manufactured highly consistently on a large scale in a limited number of countries mastering the technology. However, lack of access globally to safe and effective plasma-derived or recombinant products is particularly affecting patients with hemophilia A, von Willebrand Disease and fibrinogen depletion/dysfunction in the developing world. According to the World Federation of Hemophilia, 75 to 80% of all patients with hemophilia lack access to any form of treatment and this figure has not changed in the last 20-30

years. Additionally, inability to provide replacement for fibrinogen is a leading cause for mortality in massive hemorrhage including maternal hemorrhage at childbirth.

Considering that the existing situation of product shortage is expected to continue, it is clear that commercial CFC will remain unavailable for the treatment of patients with bleeding disorders in the foreseeable future especially in low and medium development index countries.. Therefore, alternative and realistic product alternatives need to be seriously considered.

Technologies are available that can enable local production in existing blood centers of Cryo-VI from relatively small pools of plasma or "native" cryoprecipitate units as alternatives in situations where commercial CFC concentrates are unavailable or in short supply. Indeed, several pathogen reduction technologies are available (using amotosalen with illumination, riboflavin with illumination or solvent-detergent) and have been validated for virus-inactivation of fresh frozen plasma, from which Cryo-VI could be prepared. One method is also validated for pathogen reduction of mini-pools of cryoprecipitate by solvent-detergent. Heat treatment of lyophilized cryoprecipitate was used historically in Thailand. National programs for local production and use of Cryo-VI have been implemented in Egypt, and are now considered in Indonesia and several other countries.

Therefore, the implementation of these technologies should be considered in developing countries, consistent with a comprehensive assessment of the existing need for these products and the feasibility to provide them in a quality assured system and on an appropriate national scale.

Besides the risk of acquiring transfusion transmissible infections (TTI), patients with hemophilia A in developing countries face yet another substantial risk associated with the development of inhibitors (or neutralizing allo-antibodies) which is triggered in at least 25-35% of previously untreated patients (PUPs) with severe hemophilia A and constitutes nowadays the most serious threat for these patients. On the other hand, historical epidemiological data support the fact that the clinical use of cryoprecipitate appears to be associated with a significantly lower incidence of inhibitors as compared to CFC and clinical experience with solvent/detergent treated cryoprecipitate seems to confirm its low immunogenicity. Using Cryo-VI early in the treatment of PUPs with severe hemophilia A living in developing countries could notably reduce the risk of inhibitor formation, which is often a potentially life-threatening complication particularly hard to treat in resource limited countries where products to help managing such severe clinical situations are currently lacking.

General Recommendations:

1. A situation assessment and gap analysis should be undertaken to provide a clear and comprehensive understanding of the needs, challenges and opportunities in the country regarding safe blood products, including those needed for patients with clotting disorders.
2. The results and conclusions of these critical analyses should orient the country in identifying best options for its population and making judicious choices for policies and strategies to address risks and unmet needs (i.e. choice of treatment schemes and therapeutic products).

3. Such an assessment and analysis should be conducted at the national level with consideration of internationally recognized quality and safety standards.
4. Where gaps exist in blood product supply, availability, accessibility and affordability, different product options and alternatives need to be identified, discussed and recommended to best serve the patients with bleeding disorders.
5. National capacity for local preparation of safe blood products should be encouraged and strengthened based on the situational assessment and gap analysis.
6. Existing blood establishments in developing countries should improve their operations and processes, reaching such levels that blood products can be prepared safely and continually, including use of virus reduction technologies whenever achievable.
7. A realistic action plan should be elaborated following and based on such an assessment and analysis and put in place with full support from government, to address identified weaknesses and deficiencies and to implement appropriate corrective actions at the level of blood regulation and blood component preparation.
8. Adequate human and financial support for local production of safe blood products should be provided by government, both to the regulatory authority and to blood collection establishments.
9. Manufacturers should further develop existing virus reduction technologies. Several are licensed for plasma or/and platelets but not yet for direct treatment of cryoprecipitate. A need exists for industry to make these technologies suitable also for treatment of cryoprecipitate and to obtain approvals from regulatory authorities.

Specific Recommendations:

1. Bleeding disorders such as hemophilia A, von Willebrand Disease and fibrinogen abnormalities are largely under-diagnosed. Therefore, diagnosis of these disorders should be improved (e.g. through awareness campaigns, enhanced supply of diagnostic laboratory reagents and equipment as well as education and training of medical, technical and nursing personnel).
2. Safety and quality, supply and availability, accessibility and affordability of treatment products for patients with bleeding disorders are critical issues in developing countries. "Native" cryoprecipitate can be used to treat hemophilia A, von Willebrand Disease and fibrinogen abnormalities in the absence of commercial concentrates. However, Cryo-VI should be provided because the use of non-virus-inactivated cryoprecipitate exposes patients to high risks of acquiring transfusion transmitted virus infections that can be prevented.
3. Treatment recommendations on products and regimens for patients with bleeding disorders in the developing world should be tailored to the country situation and be appropriate to satisfy clinical needs.
    a. If commercially produced CFC are available, preference should in principle be given to CFC over Cryo-VI. Nonetheless, inhibitor formation appears to be a frequent and severe adverse reaction or side-effect of some CFC (recombinant and plasma-derived) and costs for CFC are a significant burden for patients and for society. These risks need to be considered seriously when making a choice for therapeutic products to be used in resource-limited countries to treat patients with bleeding disorders.

b. If commercially produced CFC are not available for whatever reason to adequately treat patients with bleeding disorders in the country, alternative therapeutic products should be taken into consideration. In such cases, locally prepared Cryo-VI can be provided as replacement therapy and prophylaxis for patients with hemophilia A and von Willebrand Disease, and as treatment for fibrinogen dysfunction/depletion including in massive hemorrhage.

4. Pathogen reduction technologies can virtually eliminate the risk of transfusion transmitted infections (basically, those due to plasma-borne viruses). Virus inactivation techniques are available to render safe the blood products containing clotting factors. They can be integrated into routine operations of the blood establishments and allow continual local production of Cryo-VI.
5. Experience should be gained with local production of Cryo-VI in developing countries through pilot programs before there is widespread use. For example, experience is needed with organizational and technical aspects, regulatory oversight of needed medical devices, logistics, funding and reimbursement. Pilot projects on local production of Cryo-VI should be conducted at a defined number of sites selected as representative for the situation in the country.

Summary:

The conditions of treatment of patients with hemophilia A, von Willebrand Disease, fibrinogen deficiency (particularly in maternal hemorrhage) in LDI and MDI countries are unacceptable and must change. Preparation of Cryo-VI can be integrated into routine operations of blood collection establishments allowing local production of virus-inactivated cryoprecipitate from small pools of plasma or cryoprecipitate. Local preparation of Cryo-VI can help alleviate existing product shortages or lack of supply, and increase the viral safety of blood products in LDI and MDI countries, and therefore should be considered as a local alternative to commercial CFC when these products are unavailable or unaffordable.

References:

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