Prothrombin Complex Concentrates in Pediatric Cardiac Surgery: The Current State and the Future

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Background. **After decades of practice of pediatric cardiac surgery, postoperative bleeding due to the immaturity of hemostasis, hemodilution, and hypothermia remains a concern. Recently, a new approach for adult coagulopathy after bypass has emerged. Prothrombin complex concentrates (PCCs), designed to treat bleeding in hemophilia patients, are safely and efficiently used off label for hemorrhage after bypass. However, optimal dosing, indications and contraindications, and laboratory tests to assess the efficacy of PCC use in children have not yet been established. This literature review outlines the challenges of bypass-related coagulopathy, the pharmacology, and the experience in use of PCCs, with a focus on their potential in pediatric cardiac surgery.**

Methods. **After a thorough literature search of MEDLINE, Scopus, and Ovid databases using the term "prothrombin complex concentrate AND pediatric," 23 relevant articles were selected.**

Results. **The data supporting successful use of PCCs in acquired coagulopathy after cardiac surgery in adults have been increasing. Although small volume, low immunogenicity, efficiency, and speed in correcting coagulopathy are attractive qualities of PCCs for pediatric practice, current evidence is only anecdotal. The main concerns are unknown dosing regimens, the inability to closely monitor the effects of PCCs in real time, and a possibility of thrombotic complications, which can be particularly devastating in young congenital cardiac patients whose lives frequently depend upon the patency of artificial shunts.**

Conclusions. **Extensive, high-quality research is warranted to fill in the gaps of knowledge regarding using PCCs in pediatric cardiac practice.**

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Despite nearly 7 decades of growing experience in pediatric cardiac surgery, excessive bleeding still contributes to morbidity and mortality in this patient population. According to a 2009 audit undertaken in Australia, 79% of pediatric cardiac surgical patients were transfused perioperatively [1]. A similar rate of transfusions was reported by British investigators in 2015 [2]. The immaturity of the hemostatic system, combined with hemodilution and coagulopathy due to hypothermia and a relatively large cardiopulmonary bypass (CPB) circuit prime, predispose pediatric patients to a more substantial blood loss than adult patients.

Recently, a new hemostatic approach has emerged in adult practice. In many European countries and now in the United States, prothrombin complex concentrates (PCCs) are used to restore deficient clotting factors after CPB in addition to or instead of fresh frozen plasma (FFP). Historically, PCCs were designed to help hemophilia patients, especially those with antibodies to clotting factors, for treating life-threatening bleeding. Specifically, starting in the early 1970s, PCCs were used for factor IX replacement in patients with hemophilia B [3]. Since then, indications for PCCs have broadened. They were approved for the urgent reversal of Coumadin (Bristol-Myers Squibb, New York, NY), and were found to be more effective and safe than FFP in the presence of major bleeding [4–6]. More and more frequently, PCCs are successfully used off label with hemostatic purposes as a supplement to transfusion protocols in adult cardiac surgery.

The safety, efficacy, and relative cost effectiveness of PCCs demonstrated in adult patients make them an attractive option for hemostatic management in pediatric cardiac surgery. This review will outline the challenges of hemostatic management in pediatric patients, the pharmacology of PCCs, and the current experience in off-label PCC use for life-threatening bleeding in adults and children, with a focus on PCC potential in pediatric cardiac surgery.

Material and Methods

Literature searches of the MEDLINE, Scopus, and Ovid databases (including the Cochrane Database of Systematic Reviews) were conducted using the search term "prothrombin complex concentrate AND pediatric." No data

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
FEIBA = factor eight inhibitor bypassing activity
4F = four factor
FFP = fresh frozen plasma
INR = international normalized ratio
PCC = prothrombin complex concentrate
ROTEM = rotational thromboelastometry
TEG = thromboelastography
3F = three factor

limitations were set, and no other filters were applied. As of February 10, 2017, 264 search results were returned. Citations listed in the returned articles were examined for additional relevant items. Twenty-three articles describing the clinical experience with PCC use to treat coagulopathy in patients younger than 18 years of age unaffected by hereditary bleeding disorders (including hemophilia), mainly focusing on cardiac surgical patients, were included in this review.

Results

Hemostasis in Pediatric Patients, Clinical Relevance

The pediatric hemostatic system differs from that of adults. It continues to develop during the first year of life into late adolescence. Although the coagulation system of full-term neonates is balanced and fully functional, the levels of many clotting factors and inhibitors are low [7, 8]. Prothrombin levels are 20% lower in infants than in adults. Even though fibrinogen values are within the normal range, a dysfunctional fetal form with a decreased fibrin-transforming capacity may persist. There is a 50% deficiency of vitamin K–dependent factors in neonates compared with adults; high-molecular weight factors (XI, XII, prekallikrein, and kininogen) are also 50% lower. Furthermore, children with congenital heart disease, particularly cyanosis, often present with hemostatic abnormalities related to liver dysfunction and decreased factor synthesis [9]. That may explain the increased vulnerability to any derangement of coagulation.

Coagulopathy in Children After Separation From Cardiopulmonary Bypass

After separation from CPB, coagulopathy due to quantitative (dilutional) and qualitative (functional) reductions of platelets and coagulation factors can occur. Chan and colleagues [10], in a group of children older than 1 year, demonstrated a decline of coagulation factors of more than 50% immediately after initiation of CPB. Also, during CPB the platelet count decreased and bleeding time increased disproportionally, suggesting an acquired platelet dysfunction. The current standard of care to restore hemostasis after CPB is through the transfusion of allogeneic blood products. That does not guarantee the return of coagulation to baseline, and many patients require additional transfusions postoperatively. Neonatal transfusion requirements may often exceed 1 to 2 blood volumes, with the potential for volume overload and cardiopulmonary complications. Owing to the safety concerns and effects on the immune system (eg, alloimmunization) associated with blood product administration, the search for other options to treat post-CPB bleeding in children remains an important challenge.

Components of PCCs

Prothrombin complex concentrates are produced by ion-exchange chromatography from the cryoprecipitate supernatant of large plasma pools. They represent a mixture of lyophilized purified human plasma–derived vitamin K–dependent factors containing standardized concentrations of factor II (prothrombin), factor VII, factor IX, and factor X. Prothrombin and factor X have longer half-lives (40 to 72 hours) compared with the other factors in PCCs. The potency of PCCs is historically standardized to factor IX content, approximately 500 IU per vial. There are so-called "three-factor" (3F) and "four-factor" (4F) PCCs. Three-factor PCCs contain negligible amounts of factor VII relative to factors II, IX, and X. Bebulin (Baxter International, Deerfield, IL) and Profilnine (Grifols Biologicals, Los Angeles, CA) are 3F PCCs, whereas Kcentra (CSL Behring, Marburg, Germany) and factor eight inhibitor bypassing activity (FEIBA [Baxter International]) are 4F PCCs available for use in the United States. FEIBA contains an activated factor VII (factor VIIa), whereas factors in all other PCCs are inactive. In addition to clotting factors, several anticlotting substances were added to the formulations, including protein C, protein S, and heparin (Table 1). Other proteins are removed and PCCs are pasteurized to reduce the risk of transmission of transfusion-associated viral infections. The final product is a powder, not requiring cross matching. Overall, the content of PCCs is not standardized between manufacturers, but the concentration of factors is about 25 times higher than that found in FFP [11]. Reviews by Tanaka and associates [6, 12] provide tables of the content of several PCCs available worldwide.

Mechanism of Action

Prothrombin complex concentrates induce thrombin generation, with a subsequent transformation of fibrinogen to fibrin. The fibrin polymerization defect is the primary target of PCCs, and the enzymatic defect is addressed after hypofibrinogenemia and, ideally, fibrinolysis are corrected [13]. It is essential to make sure that the patient does not receive the dose of PCC before a normalizing fibrinogen level.

Advantages of PCC Over FFP

The universal compatibility and room temperature storage of PCCs allow for rapid reconstitution without the need for ABO typing and product thawing. Only a small volume has to be infused when giving PCCs compared with FFP for similar levels of coagulation factors, reducing the risk of transfusion-associated circulatory overload and of erythrocytes dilution. Transfusion of large fluid