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Original Article

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Prothrombin Complex Concentrate to Treat Coagulation Disturbances in Pediatric Patients With Intracranial Pathology Including Traumatic Brain Injury

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Abstract

Background: Coagulation disturbances and hemorrhage are common in critically ill pediatric patients especially those with intracranial pathology or traumatic brain injury (TBI). Even with therapy directed by laboratory parameters, blood products may fail to effectively correct the underlying coagulation defect. To mitigate these challenges, various adjunctive agents including prothrombin complex concentrates (PCCs) have been used in patients who have coagulation disturbances refractory to standard therapy. However, data regarding the use of PCCs in pediatric-aged patients are limited.

Methods and Results: We retrospectively identified 47 critically ill pediatric patients, ranging in age from 1 day to 18 years, with intracranial pathology including TBI who received PCC. The primary clinical indications for four-factor PCC (4F-PCC) were surgical procedures, hemorrhage control, or intracranial pressure monitor placement. A total of 71 doses of 4F-PCC were administered to the 47 patients in the study cohort. The PCC dose ranged from 11 to 75 units/kg (median dose 26 units/kg). The majority of patients (n = 35, 75%) received one dose of 4F-PCC while 12 patients received more than one dose. Following the administration of PCC, there was a correction in laboratory assessment of coagulation function (international normalized ratio and prothrombin time) with a limited effect on partial thromboplastin time. Because of the severity of illness and limitations of controlling confounding variables in a retrospective study, additional information on the direct effects of 4F-PCC on patient outcome including blood product utilization was limited.

Conclusions: Given the increasing use of PCC in pediatric-aged patients and its potential utility in life-threatening scenarios, additional clinical trials are needed to define clinical indications, dosing regimens, and optimal monitoring techniques.

Keywords: Prothrombin complex; Coagulopathy; Bleeding; Traumatic brain injury; Neurosurgery; Surgery; Trauma

Introduction

Coagulation disturbances and hemorrhage are common in critically ill pediatric patients especially those with intracranial pathology or traumatic brain injury (TBI). Various etiologies predispose these patients to bleeding diathesis including blood loss, large volume transfusions, shock, coagulation factor consumption, hypothermia, acidosis, and release of tissue factors from the injured brain [1]. Clinical management strategies include addressing the physiologic needs of the patient with correction of cardiovascular dysfunction, treatment of systemic infection, attention to the associated traumatic injury and resultant acquired coagulopathy, and correction of pre-existing anti-coagulant therapies or inherited disturbances of coagulation. Based on laboratory parameters, treatment pathways for the reversal of coagulation disturbances include transfusion of blood products including fresh frozen plasma (FFP), cryoprecipitate, and platelets [2]. However, the administration of blood products and FFP has several potential limitations including the time required to prepare, thaw, and transfuse it, the risk of transfusion reactions, and an increased incidence of secondary infections, organ failure, pulmonary complications, and even mortality [3, 4]. Furthermore, even with therapy directed by laboratory parameters, these blood products may fail to effectively correct the underlying coagulation defect. Delays in coagulopathy correction may result in delays in diagnostic or therapeutic interventions.

Recently, the anecdotal use of prothrombin complex concentrates (PCCs) has been increasingly reported in adults and children as therapy for the correction of refractory coagulation disturbances in various clinical scenarios [5, 6]. PCCs available for clinical use can be separated into three-factor PCCs (3F-PCCs), four-factor PCCs (4F-PCCs), and PCCs with activated factors such as factor eight inhibitor bypassing activity (FEIBA). Availability of the specific products for clinical use varies according to country of practice. The currently available 4F-PCCs contain coagulation factors II, VII, IX, and X

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Table 1. Demographic Data of the Study Cohort

Parameter	Mean ± SD with range or number
Number	47
Age (years)	8.97 ± 6.78, 1 day to 18 years
Weight (kg)	35.44 ± 27.11, 3.2 to 96.5 kg
Gender (male/female)	29/18

SD: standard deviation.

in addition to proteins C and S and antithrombin III [7]. Four-factor PCCs were initially used in patients with hemophilia B or those with hemophilia A who had developed inhibitors to standard therapy with factor VIII products. Four-factor PCCs are now also considered first-line therapy for adults who are chronically receiving oral vitamin K antagonist who present with clinically significantly bleeding or require urgent/emergent surgical interventions [6, 8, 9]. We present our retrospective experience with the use of 4F-PCC in patients with neurosurgical conditions, intracranial pathology, and TBI.

Materials and Methods

This retrospective study was reviewed and approved by the IRB of Nationwide Children's Hospital (Columbus, OH) and conducted in accordance with the guidelines of the Declaration of Helsinki. Given the retrospective nature of the study, the need for individual written informed consent was waived. The waiver of consent was based on the fact that the research involved no or minimal risk since it was limited to a retrospective chart review. To maintain patient confidentiality, only deidentified data were used for the purpose of this study. Data collected during this study were stored in a secure location and only the collaborators directly involved in this study have access. All electronic files were stored on a secure, password protected network. This study expands on our previously published work by focusing specifically on patients with associated intracranial pathology and by expanding the study database with a longer duration of the retrospective review [5]. The current study includes patients who were reported in our previous study if they had associated intracranial pathology.

Patients who received 4F-PCC (K-Centra®, CSL Bering, King of Prussia, PA) were identified by the Pharmacy Services and the medication records of the hospital's electronic medical record (EMR) database. The study cohort was limited to patients 0 - 18 years of age who have received 4F-PCC in the setting of TBI, intracranial pathology, or other central nervous system (CNS)-related neurosurgical disorders. The study period included a 13-year period spanning from January 2010 through December 2022. Data regarding demographics, surgical procedures, clinical information, laboratory and radiographic results, administered blood products before and after 4F-PCC, and 4F-PCC dosing were retrieved from the EMR. Clinical efficacy was judged by coagulation parameters, blood product use, and clinical bleeding before and after the administration of 4F-PCC. Adverse effects related to 4F-PCC including thromboembolic complications and survival outcomes were also collected.

Table 2. Primary Etiology of Coagulation Disturbance

Etiology	N (%)
Intracranial hemorrhage	24 (51%)
Increased intracranial pressure/ hypoxic-ischemic encephalopathy	13 (28%)
Traumatic brain injury	7 (15%)
Hemorrhagic shock	3 (6%)

Demographic and laboratory data are presented as mean ± standard deviation (SD) and the range. Dosing information is presented as mean and interquartile range (IQR). Statistical analysis included a paired *t*-test to compare coagulation parameters including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) before and after the administration of 4F-PCC.

Results

The study cohort included 47 patients, ranging in age from newborn to 18 years, who were diagnosed with TBI or other intracranial pathology (e.g., hemorrhage), and who received 4F-PCC. The demographic data are outlined in Table 1. The average patient was 8.97 ± 6.78 years of age with a range from newborn (1 day) to 18 years. The average patient weight was 35.4 ± 27.1 kg with a range of 3.2 to 96.5 kg. The primary etiology of the coagulation disturbance included intracranial hemorrhage (n = 24, 52%), increased intracranial pressure or hypoxic-ischemic encephalopathy (n = 13, 28%), TBI (n = 7, 15%), and hemorrhagic shock (n = 3, 6%) (Table 2). The primary clinical indications for 4F-PCC administration included the presence of or potential for ongoing bleeding with an associated coagulopathy in the setting of a neurosurgical procedure (n = 23, 49%), to prevent ongoing hemorrhage or mitigate the potential for expansion of an intracranial hemorrhage (n = 17, 36%), or the combination of the two (n = 7, 15%). Multiple patients (n = 32, 68%) in the current cohort received FFP within 6 h of the 4F-PCC dose. Additional blood products used around the time of 4F-PCC administration included packed red blood cells (n = 18, 38%), cryoprecipitate (n = 5, 11%), or platelets (n = 15, 32%).

A total of 71 doses of 4F-PCC were administered to the 47 patients in the study cohort. The dose ranged from 11 to 75 units/kg (median dose 26 units/kg; mean dose 30.4 ± 14.7 units/kg) (Table 3, Fig. 1). The majority of patients (n = 35, 75%) received one dose of 4F-PCC. The remaining 12 patients received multiple doses. Two doses were administered to seven patients (15%), three doses to two patients (4%), four doses to one patient (2%), five doses to one patient (2%), and seven doses to one patient (2%). Varied indications existed for the use of multiple doses including further correction of coagulation parameters, control of ongoing bleeding, or an anticipated or ongoing surgical procedure.

Laboratory assessment of coagulation function generally improved after the administration of 4F-PCC. INR values decreased after the administration of 4F-PCC for 78% of doses, with 38% of INR values decreasing from an abnormally high

Table 3. Dosing of 4F-PCC in the Study Cohort

Parameter	Dose (units/kg)
Range	11 - 75
Median	26
Mean ± SD	30.4 ± 14.7
IQR	20.5 - 38.8 (18)

Dose (units/kg)	Frequency
< 20	14 (20%)
20 - 29	34 (48%)
30 - 39	7 (10%)
40 - 49	3 (4%)
50 - 59	10 (14%)
≥ 60	3 (4%)

Frequency is based on percentage of the total of 71 doses. 4F-PCC: four-factor prothrombin complex concentration; IQR: interquartile range; SD: standard deviation.

value into the normal range (≤ 1.5) (Table 4). PT values decreased after 4F-PCC in 74% of doses; however, only 1.6% of PT values decreased from an abnormally high value into the normal range (≤ 15 s). PTT values decreased after 4F-PCC administration in 63% of doses with 16% decreasing from an abnormally high value into the normal range (≤ 35 s). The INR decreased from 2.4 ± 1.4 before 4F-PCC to 2.0 ± 1.5 after 4F-PCC. The PT decreased from 25 ± 11 s before 4F-PCC to 22 ± 11 s after 4F-PCC while no change was noted in the PTT. Thirty-one patients (66%) underwent a surgical procedure around the time that 4F-PCC was administered. The surgical procedures included craniectomy, craniotomy, burr hole placement, cranial decompression, and hematoma evacuations.

Table 4. Laboratory Coagulation Parameters Before and After 4F-PCC

Coagulation parameter	Parameter decreased	Corrected to normal value*	Value (s) before and after 4F-PCC**
INR	78%	38%	2.4 ± 1.4 to 2.0 ± 1.5, P = 0.11
PT	74%	1.6%	25 ± 11 to 22 ± 11, P = 0.03
PTT	63%	16%	63 ± 48 to 70 ± 60, P = 0.36

*Percentage based on numbers that were high prior to 4F-PCC. **Paired *t*-test, P < 0.05 was considered significant. 4F-PCC: four-factor prothrombin complex concentration; INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time.

Adverse effects that may have been attributed to 4F-PCC were noted in three of 47 patients (6.4%). These adverse events, each occurring in one patient, included thrombotic complications of the common femoral and iliac veins, external iliac artery, or internal carotid artery. Overall, the severity of illness was significant with an overall patient mortality of 53% in this patient population related to coagulopathies, associated with immature hemodynamic stability, TBI, hemorrhages, or other neurosurgical disturbances.

Discussion

TBI and intracranial pathologies associated with coagulopa-

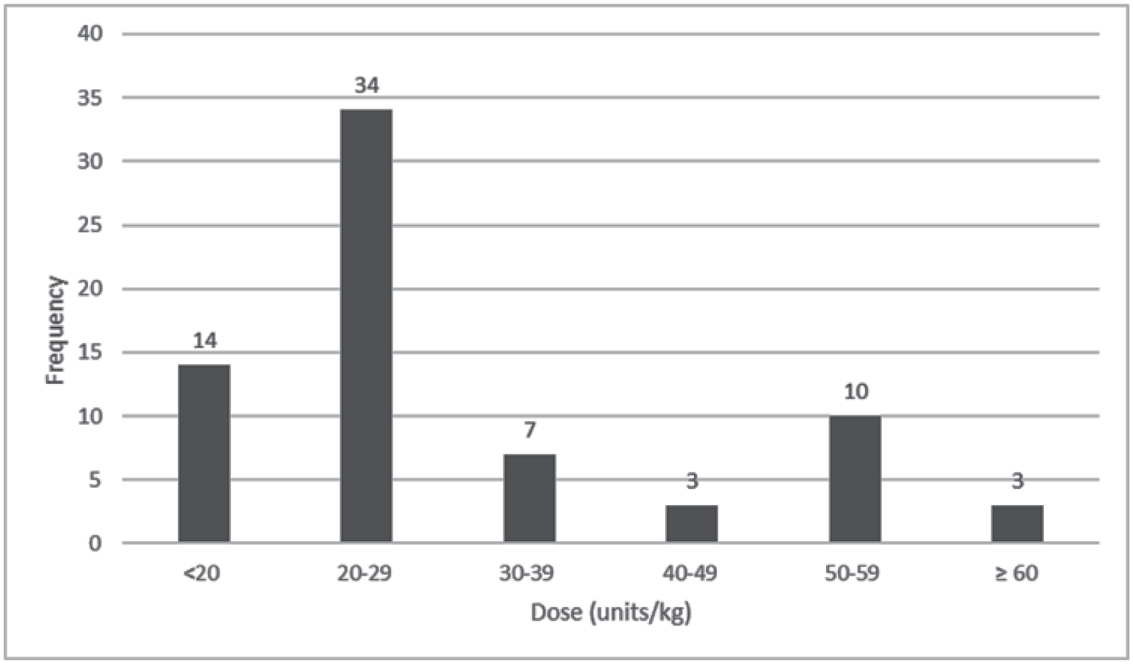

Figure 1. Histogram showing distribution of the 71 doses of 4F-PCC in the cohort of 47 patients with the dose in units/kg on the x-axis and the number of doses on the y-axis. 4F-PCC: four-factor prothrombin complex concentration.

thy remain common causes of morbidity and mortality in critically ill infants and children. The primary etiologies of these coagulation disturbances are multi-factorial including blood loss, transfusion of blood products with dilution of coagulation factors, coagulation factor consumption, and the release of thrombogenic factors with TBI and intracranial pathology. The coagulation disturbances can be further accelerated by hypothermia, liver dysfunction, hypoperfusion, and metabolic acidosis [1]. Traditionally, FFP, cryoprecipitate, and platelet concentrates remain the primary method to treat and reverse coagulation disturbances with administration based on laboratory parameters [2]. However, in addition to potential adverse effects, additional limitations include treatment delays related to preparation time with cross-typing, thawing, and transfusion as well as ineffective correction of coagulation defects despite appropriate dosing [2-4]. Contemporary alternatives with anecdotal reports of success primarily in case series of trauma or cardiac surgical patients include single factor concentrates or more recently, PCCs [10-14].

The currently available 4F-PCCs contain coagulation factors II, VII, IX, and X in addition to proteins C and S and antithrombin III. In addition to their clinical indications in specific scenarios in patients with hemophilia, they are considered first-line therapy for adults who are chronically receiving oral vitamin K antagonists who present with clinically significantly bleeding or require urgent/emergent surgical interventions [8, 9]. Three-factor PCCs are generally used to treat hemophilia B. Outside of these scenarios, clinical experience with PCCs in children has generally focused on controlling bleeding following cardiopulmonary bypass and surgery for congenital heart disease [15-20]. Outside of the cardiac surgery population, there are a limited number of reports regarding the use of 4F-PCC in pediatric-aged patients. A unifying theme of some of the studies is a focus on preterm infants with the administration of PCCs as a means to control or limit the extent of intracranial hemorrhage related to prematurity or associated hypoxic-ischemic encephalopathy [21]. In a meta-analysis of these reports, Zeng and colleagues analyzed three randomized controlled trials, three non-randomized controlled trials, and two cohort studies [21]. The meta-analysis failed to find that PCC improved mortality or more effectively corrected hemostatic defects.

Our study expands upon the previous work of Karube et al, specifically focusing on patients with intracranial pathology and associated coagulation dysfunction [5]. We noted a correction of coagulation values when 4F-PCC was administered in pediatric patients presenting with coagulopathy related to TBI, intracranial pathologies, and neurosurgical disorders. When assessing routine coagulation parameters to judge efficacy, the response was variable. Overall, INR values decreased in 78% of patients, PT values decreased in 74% of patients, and activated PTT (aPTT) values decreased in 63% of patients; however, the change was a statistically significant decrease only when considering PT. Furthermore, given the variability in the dose and perhaps the lack of strict dosing guidelines, the majority of the laboratory values of coagulopathy did not correct to normal. Because of the severity of illness and limitations of controlling confounding variables in a retrospective study, additional information on the direct effects that 4F-PCC might have had on patient outcomes, including blood product utilization, was limited.

There were multiple limitations to the current study starting with a small, retrospective sample size. Although we attempted to focus on a specific population (intracranial pathology), there was still significant heterogeneity in our patients, the primary event responsible for the coagulation disturbances, the indication for PCC, and the dose. As in most pediatric studies, there was significant variation in patient age, weight, and ethnicity with a range of comorbid diseases. There were no specific guidelines regarding indication for 4F-PCC, blood product use prior to giving 4F-PCC, or interpretation of laboratory parameters before and after use. The confounding treatments limited the ability to objectively assess the sole effectiveness of 4F-PCC in the reversal of coagulopathies and hemorrhagic disturbances related to TBI. The circumstances regarding patient conditions varied greatly, with many doses of 4F-PCC being administered to critically ill patients in dire conditions, affecting the apparent efficacy of using 4F-PCC for the treatment of coagulopathies due to TBI. Many of these same confounders were present with the initial studies reporting the use of recombinant factor VIIa [22, 23]. These same limitations apply to identification of adverse effects. With a retrospective chart review, it is possible that adverse effects may not have been charted, may be missed during the review or a cause-effect relationship related to therapies may be difficult to determine.

Moving forward, patient care and research on this topic might be improved with internal guidelines regarding both indications for use and for initial and subsequent dosing parameters. To better analyze its efficacy, future studies could be conducted using randomized controlled trials in pediatric populations with TBI and intracranial pathologies to accurately identify indications, proper dosages, and potential adverse effects. The standardization of dosing and parameters within a homogenous population will allow direct analysis of the effectiveness of 4F-PCC. As noted in our study cohort, there was significant variation in dosing, ranging from 11 to 75 units/kg with a median dose of 26 units/kg. There are no specific dosing guidelines when 4F-PCC is used to correct generalized coagulopathy related to systemic illnesses. When used to reverse anticoagulation related to oral vitamin K antagonist, recommendations for dosing are based on the INR with a dose of 25 units/kg (maximum dose 2,500 units), 35 units/kg (maximum dose 3,500 units), or 50 units/kg (maximum dose 5,000 units) for an INR value of 2 - 4, 4 - 6 or more than 6, respectively.

Due to the severity of hemostatic disturbances in pediatric patients with intracranial pathologies, larger doses of PCC may be necessary to truly assess the clotting potential of the drug; however, adverse reactions, such as thromboembolic events, need to be monitored. There is also potential for more precise coagulation parameters with the use of thromboelastometry (ROTEM) and thromboelastography (TEG), along with traditional INR, PT, and aPTT to quantify total clotting capacity [24]. The cost-benefit analysis of 4F-PCC is uncertain due to the conflicting balance between cost of therapy (cost of 4F-PCC) and cost of transfusion including type and screen, blood acquisition and processing costs, and transfusion costs. Four-

factor PCC, when compared to FFP may be associated with a higher cost of therapy when considering only the product, but possesses lower costs of overall therapy including additional costs involved with transfusion.

In conclusion, the current study found decreased coagulation values when 4F-PCC was administered in pediatric patients presenting with TBI, intracranial pathologies, and CNS neurosurgical disorders. However, due to the retrospective nature of the study, no direct conclusions were able to be established regarding the effects of 4F-PCC. Although small volumes, low immunogenicity, efficiency, and speed in correcting coagulopathy are attractive qualities of PCCs for pediatric practice, current evidence remains anecdotal. The main concerns are unknown dosing regimens, lack of an identified clinical means to monitor the effects of PCCs in real time, and the possibility of thrombotic complications. Future randomized controlled trials should be utilized to establish effective doses for PCC in pediatric patients based on clinical and laboratory parameters, identify optimal protocols to define indications for PCC, define optimal laboratory parameters to evaluate clinical efficacy, and monitor for adverse effects. The need for such trials is demonstrated by the increasing off-label use of PCCs over the past 4 years in pediatric patients, especially in critically ill patients with a high risk for mortality [25].

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Given the retrospective nature of the study, the need for individual written informed consent was waived.

Author Contributions

CR: chart review and preparation of manuscript; EAS: study design and review of the final manuscript; JDT: study design, manuscript preparation, review, and editing.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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