Prothrombin Complex Concentrates for Coagulopathy in Liver Disease: Single-Center, Clinical Experience in 105 Patients

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Patients with liver disease frequently develop coagulopathy, and fresh frozen plasma is traditionally used for correction of coagulopathy to manage and prevent bleeding. Prothrombin complex concentrates (PCCs) offer an attractive alternative because they are more readily available and avoid large-volume transfusion. This retrospective, single-center study reviewed clinical use of PCC in patients with acute/chronic liver disease. A total of 105 patients with 194 episodes of PCC administration were reviewed. Data pertaining to indication, dosing, effectiveness, and safety were collected. The effect of PCC on coagulation was analyzed in patients for whom coagulation results were available 7 hours before and after PCC. Data on thromboembolic events and mortality within 4 weeks of PCC administration were captured. Most patients (77%) had chronic liver disease; the remainder had acute liver failure. Indications for PCC were preprocedure prophylaxis and treatment for active/recent bleeding in 48% and 52% of 194 treatment episodes, respectively. The median dose of PCC administered was 22 IU/kg (interquartile range, 16-29 IU/kg). Before PCC administration, 45% of patients had an international normalized ratio (INR) greater than 2.0, and 36% had fibrinogen levels of at least 1.5 g/L. PCC produced statistically significant reductions in prothrombin time and INR (coadministration with fibrinogen or cryoprecipitate: 3.1 versus 1.9; $P < 0.001$; no coadministration: 2.3 versus 1.8; $P < 0.001$). Three patients with multiple risk factors developed thrombotic events (hepatic artery thrombosis, incidental bilateral pulmonary embolism, nonocclusive portal vein thrombosis); there were no cardiovascular or cerebrovascular adverse events. Overall, 46 patients died of causes unrelated to PCC treatment. *Conclusion:* In patients with liver disease, PCC therapy was effective in improving coagulation test results without an excess of thrombotic events. Further assessment of PCC as hemostatic therapy in this setting is required. (*Hepatology Communications* 2019;3:513-524).

Liver disease is the fifth most common cause of death in the United Kingdom.[(1)] Hospital admissions and deaths relating to liver disease are rising, with guidelines highlighting the need for improving the management of patients who present with bleeding complications relating to portal

Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; PCC, prothrombin complex concentrate; PT, prothrombin time; and rFVIIa, recombinant activated factor VII.

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hypertension and coagulopathy or need an invasive procedure (e.g., diagnostic workup or therapeutic surgery).[2,3]

Liver failure encompasses a wide spectrum of liver diseases, ranging from progressive chronic disease to *de novo* acute liver failure. It is increasingly acknowledged that patients with chronic liver disease have dysregulated coagulation with an increased risk of thrombosis as well as diminished hemostatic reserve, meaning they are likely to decompensate early during bleeding.[4-6] Similar hemostatic abnormalities are observed in acute liver failure.[7] Regardless of the nature of the disease, hemostatic derangements are common and include decreased plasma levels of procoagulants and anticoagulants due to decreased synthesis and a low platelet count/impaired platelet function.[8,9] As a result, patients with liver disease undergoing surgery may be at risk of thrombosis as well as bleeding.[7,10,11] Spontaneous bleeding is uncommon and infrequently observed in clinical practice, and bleeding risk is primarily procedure related.

In the context of bleeding, early replenishment of coagulation factors may be required due to the diminished reserve. Patients with liver disease who have abnormal prothrombin time (PT) and elevated international normalized ratio (INR) may receive replacement therapy with fresh frozen plasma (FFP), either prophylactically to prevent bleeding in the context of procedures or for bleeding related to underlying liver disease. Where clinically indicated, FFP is the current standard of care for the management of coagulopathy to treat active bleeding or for prophylaxis before an invasive procedure.[12-15] Typically, an FFP dose of 15 mL/kg is suggested for correction of coagulopathy[16]; however, patients with liver disease may not tolerate this volume, which creates a significant barrier to effective treatment with FFP.

In the United Kingdom and Europe, prothrombin complex concentrates (PCCs) have a broad license for treatment and prophylaxis of bleeding in acquired deficiency of PCC factors.[17] PCCs consist of non-activated vitamin K–dependent coagulation factors and anticoagulant proteins C and S and have demonstrated superiority over FFP in the reversal of acquired coagulation factor deficiency induced by vitamin K antagonists.[18-20] Indeed, guidelines advocate the use of PCCs to reverse the effects of vitamin K antagonists over FFP[21] because they are concentrated, ensure consistent correction, and reduce the risk of fluid overload.[22] Because vitamin K–dependent clotting factors are also decreased in liver disease, studies have suggested a potential role for PCCs in patients with coagulopathy related to liver disease.[23-26] PCCs in this scenario have the same advantages over FFP, particularly in actively bleeding patients.[22] Because the risk of thromboembolic complications is a concern with the clinical use of PCCs (particularly when high or repeated doses are given),[27,28] PCC administration in bleeding patients is ideally guided by thromboelastogram and/or rotational thromboelastometry in addition to PT/INR; this needs to be preceded by adequate replenishment of fibrinogen.[27]

In our institution, FFP has over recent years been replaced by PCCs for managing the coagulopathy of liver disease for certain clinical scenarios. Currently, two types of PCC preparation are widely available worldwide; these contain either three factors (II, IX, and X) or four factors (II, VII, IX, and X). In this retrospective, single-center audit/service evaluation, we describe our experience of four-factor PCC use in patients with acute and chronic liver disease. Our aim was to evaluate the indications for PCC use and the correction of PT/INR at each administration. In addition, the coadministration of other products and

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safety outcomes, including the presence of thrombotic complications, was assessed.

Methods

STUDY DESIGN

This was a retrospective, single-center audit/service evaluation of the use of PCCs in patients with acute or chronic liver disease. All data were collected at the Royal Free Hospital, London, United Kingdom. Ethical review was not required because the study was considered to represent an audit of routine clinical practice with the aim of improving patient care.

All use of PCCs was recorded at the time of treatment on a form capturing patient details, indication for use, date and time of administration, dose, and baseline coagulation test results. All patients had received PCCs between January 2008 and June 2012. Data were transferred to a structured form and anonymized at the earliest opportunity.

Medical notes were reviewed, and the following data were collected: patient demographics; details of the underlying liver disease, including etiology and severity; risk factors for cardiovascular and cerebrovascular disease (e.g., hypertension, diabetes mellitus, smoking, hypercholesterolemia); and the presence of any cardiovascular or cerebrovascular disease (e.g., ischemic heart disease, coronary artery bypass graft, transient ischemic attacks, cerebrovascular accidents). History of venous thromboembolic disorders, such as peripheral deep vein thrombosis, pulmonary embolism, and thrombosis of portal and other visceral veins, was also documented.

Additional details captured for each patient included indication for admission, number of PCC administration events, concurrent hemostatic interventions (e.g., cryoprecipitate, fibrinogen concentrate, vitamin K, tranexamic acid, recombinant activated factor VII [rFVIIa], red blood cells, FFP, platelets), laboratory test results (e.g., INR [before and after PCC administration], fibrinogen levels, baseline hematology and chemistry [hemoglobin, platelet count, sodium, bilirubin]), Model for End-Stage Liver Disease scores, and Child-Pugh scores. Entries in the medical notes and radiology reports were screened for thrombotic and bleeding complications as well as mortality that occurred during the 4-week period after PCC administration. Death due to a known complication of PCC was considered as possibly related. All authors had access to the study data and the analysis.

STUDY OUTCOMES

The primary outcomes of the study were the categorization of indications for PCC administration and the ability of PCC to correct PT/INR at each administration and potential relation to the dose administered. The secondary outcome was the assessment of coadministration of other hemostatic products. Because some patients received more than one dose of PCC, safety outcomes, including thrombotic complications and mortality, were reported for each patient.

TREATMENT PRODUCTS, DOSING, AND MONITORING

The PCCs administered were Beriplex P/N (CSL Behring, Marburg, Germany) and, during 2008, Octaplex (Octapharma, Lachen, Switzerland). Beriplex and Octoplex are 4-factor PCCs that contain coagulation factors II, VII, IX, and X along with proteins C, S, and Z with variable amounts of heparin.[17,29] These products are licensed in the United Kingdom and Europe for treatment and perioperative prophylaxis of bleeding related to acquired deficiencies of vitamin K–dependent coagulation factors, and for treatment and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K–dependent coagulation factors.[17,29] Dosing of PCC was guided by coagulation test results and underlying thrombotic history. Based on experience with PCC in warfarin reversal, doses of 20 IU/kg to 25 IU/kg were administered to patients with INR less than 4.0, and 30 IU/kg for patients with INR greater than 4.0.[30] The actual dose administered was rounded to the nearest whole number of PCC vials. During prolonged inpatient stays, repeat doses were generally given over several days, or occasionally twice a day; in such instances, the INR was often used as a guide for repeat dosing. In eight instances, repeat doses were given within 7 hours. Clinicians were encouraged to send blood samples for coagulation testing just before administration of PCC and 15 to 30 minutes after administration. In keeping with the half-life of factor VII and its effect on the INR, only samples taken

within 7 hours before and 7 hours after PCC administration were included for the analyses reported here.

In accordance with hospital policy, fibrinogen concentrate or cryoprecipitate was administered when plasma fibrinogen levels were less than or equal to 2 g/L in actively bleeding patients and less than or equal to 1.0 g/L to 1.5 g/L in patients scheduled to undergo a surgical procedure.

STATISTICAL ANALYSES

Statistical analyses comparing results obtained before versus after each PCC administration were performed using the Wilcoxon matched-pairs test, except for episodes with INR less than or equal to 1.5, in which the McNemar test was used. Analyses were categorized per episode according to whether fibrinogen and/or cryoprecipitate was administered. Episodes that required coadministration of rFVIIa (n = 4) were excluded from these analyses.

Results

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT ADMISSION

Initially, 107 consecutive patients with liver disease receiving 197 PCC treatments were included; 2 of these patients, both of whom underwent hepatectomy, were excluded because underlying liver disease could not be confirmed. The final analysis therefore included 194 PCC administration events in 105 patients. Demographics of the patient population and the underlying etiology and severity of liver disease at admission are presented in Table 1. Most of the patients included had severe liver disease and coagulation abnormalities. Of the 81 patients with chronic liver disease, 18 were admitted for elective orthotopic liver transplantation, and 12 had hepatocellular carcinoma. Of the 24 patients with acute liver failure, 6 required liver transplantation.

Table 2 presents the indications for initial admission along with the severity of the liver disease and selected laboratory test results for each indication. Many patients appeared to have severe coagulopathy: 45% had an INR greater than 2.0, and 36% had fibrinogen levels of 1.5 g/L or less.

TABLE 1. DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF PATIENTS

Clinical Feature	Number of Patients (%)
Total number of patients	105
Total number of PCC treatment episodes	194
Gender	
Male	36 (34%)
Female	69 (66%)
Age	
≤ 40	25 (24%)
41-50	27 (26%)
51-60	32 (30%)
61-70	14 (13%)
> 70	7 (7%)
Type of liver failure	
Chronic liver disease	81 (77%)
Acute liver failure	24 (23%)
Chronic liver disease etiology*	
ALD	44 (42%)
PBC/PSC/AI	10 (10%)
Viral	25 (24%)
NASH	5 (5%)
CCF	4 (4%)
HCC	11 (10%)
Other	15 (14%)
Severity of liver disease at admission (Child-Pugh grade)†	
< 7 = A	4 (6%)
7-9 = B	27 (38%)
> 9 = C	40 (56%)
Severity of liver disease at admission (MELD)†	
≤ 9	4 (5%)
10-19	42 (53%)
20-29	22 (28%)
30-39	10 (13%)
≥ 40	2 (3%)
Acute liver failure etiology	
Acetaminophen overdose	11 (46%)
Viral/HBV	4 (17%)
Other	9 (38%)
Patients undergoing OLT	
Chronic liver disease	18 (17%)
Acute liver failure	6 (6%)

*Patients may have more than one etiology. Percentage values will add up to more than 100%.
†Figures based on patients with chronic liver disease only. Percentages are of those patients with available data.
Abbreviations: AI, adrenal insufficiency; ALD, acute liver disease; CCF, congestive cardiac failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

TABLE 2. SEVERITY OF LIVER DISEASE AND COAGULATION ABNORMALITIES BY ADMISSION INDICATION

Indication for Admission	No. of Patients (%)	Child-Pugh				INR			Fibrinogen				Platelets			
		A	B	C	No information	≤ 1.5	1.6-2.0	> 2.0	≤ 1.5	1.6-4.0	> 4.0	No information	< 50	51-80	> 80	No information
Chronic liver disease	81	4 (5%)	27 (33%)	40 (49%)	10 (12%)	22 (27%)	31 (38%)	28 (35%)	26 (32%)	28 (35%)	2 (2%)	25 (31%)	12 (15%)	18 (22%)	50 (62%)	1 (1%)
Decompensation	49	0	13	26	10	9	18	22	20	16	1	12	5	9	34	1
Bleeding	23	0	8	8	7	5	12	6	6	14	0	3	3	7	12	1
Septic (without bleeding)	11	0	2	7	2	1	4	6	6	1	1	3	1	0	10	0
Nonseptic (without bleeding)	15	0	3	11	1	3	2	10	8	1	0	6	1	2	12	0
Procedure (OLT excluded)	11	2	6	2	1	4	6	1	1	5	0	5	2	4	5	0
Other	3	0	0	3	0	0	1	2	1	1	0	1	3	0	0	0
OLT	18	2	8	8	0	9	6	3	4	9	1	4	2	5	11	0
Acute liver failure	24	—	—	—	—	2 (8%)	3 (13%)	19 (79%)	12 (50%)	8 (33%)	0 (0%)	4 (17%)	2 (8%)	3 (13%)	17 (71%)	2 (8%)
Conservative treatment	18	—	—	—	—	2	3	13	8	8	0	2	2	2	12	2
OLT	6	—	—	—	—	0	0	6	4	0	0	2	0	1	5	0
Total	105	—	—	—	—	24 (23%)	34 (32%)	47 (45%)	38 (36%)	36 (34%)	2 (2%)	29 (28%)	14 (13%)	21 (20%)	67 (64%)	3 (3%)

Abbreviations: OLT, orthotopic liver transplantation.

PCC ADMINISTRATION, TRANSFUSION OF BLOOD COMPONENTS, AND OTHER HEMOSTATIC THERAPIES—EPISODE-LEVEL ANALYSIS

Of the 194 PCC administration episodes assessed, 93 were for preprocedure prophylaxis (48%) and 101 (active: n = 81; recent: n = 20) for bleeding (52%). Details of PCC and concurrent hemostatic therapy in relation to preprocedure prophylaxis and bleeding (recent and active) are provided in Table 3. Hemostatic therapy administered in addition to PCC in both preprocedure prophylaxis and bleeding episodes included fibrinogen concentrate (59 of 194 episodes; 30%) and cryoprecipitate (36 of 194 episodes; 19%), with both treatments administered in 4% (8 of 194) of episodes. Patients who received PCC for active bleeding received more allogeneic blood products than those receiving PCC prophylactically, including red blood cell transfusion (58 of 81 [72%] versus 32 of 93 [34%], respectively), FFP (39 of 81 [48%] versus 25 of 93 [27%], respectively), and platelets (45 of 81 [56%] versus 27 of 93 [29%], respectively). PCC use and concurrent hemostatic therapies are further described in Supporting Tables S1 and S2, stratified by surgical procedure and bleeding category, respectively.

DOSE OF PCC PER ADMINISTRATION AND COADMINISTRATION OF OTHER HEMOSTATIC THERAPIES

Dose of PCC per administration is shown in Figure 1. The most commonly administered dose (30% of all episodes) was 1,500 IU; accordingly, the median dose was 1,500 IU (interquartile range [IQR]: 1,000-2,000 IU). With respect to body weight, the most common dose range was 21 IU/kg to 25 IU/kg, in keeping with the recommended dose for warfarin reversal in patients with INR 2.0-3.9. The median dose was 22 IU/kg (IQR: 16-29 IU/kg). Sixty-six percent of patients received a single dose of PCC, 12% received two doses, 9% received three doses, 8% received four doses, and 6% received more than four doses.

In the overall population, in addition to PCC, 35% of patients received fibrinogen concentrate, and 29% received cryoprecipitate. Fibrinogen was most frequently administered at a dose of 1 to 2 g (46% of treatment episodes), although nearly as many doses

TABLE 3. TRANSFUSION AND HEMOSTATIC THERAPY BY EPISODES IN WHICH PCC WAS ADMINISTERED AS PREPROCEDURE PROPHYLAXIS AND EPISODES IN WHICH PCC WAS ADMINISTERED FOR ACTIVE OR RECENT BLEEDING

Therapy	Preprocedure Prophylaxis (n = 93)[*,†]	Active Bleeding (n = 81)[‡]	Recent Bleeding (n = 20)[‡]
PCC dose (IU/kg)			
≤ 20	37 (40%)	23 (28%)	9 (45%)
21-30	47 (51%)	40 (49%)	9 (45%)
> 30	8 (9%)	18 (22%)	2 (10%)
PCC plus fibrinogen[§]	22 (24%)	29 (36%)	8 (40%)
Red blood cells			
None	60 (65%)	23 (28%)	16 (80%)
Transfusion	32 (34%)	58 (72%)	4 (20%
FFP	25 (27%)	39 (48%)	4 (20%)
Cryoprecipitate	13 (14%)	22 (27%)	1 (5%)
Platelets	27 (29%)	45 (56%)	3 (15%)

*For 1 patient, the specific procedure is not available.
†Supporting Table S1 provides details of therapy stratified by surgical procedure (central venous pressure, transjugular intrahepatic portosystemic shunt, hepatic embolization, paracentesis, thoracocentesis and tracheostomy, intracranial pressure bolt, orthotopic liver transplantation, other).
‡Supporting Table S2 provides details of therapy stratified by bleeding category (gastrointestinal bleeding—variceal, gastrointestinal bleeding—nonvariceal, line-related/drain-related and bleeding tumor, orthotopic liver transplantation, intracranial, trauma, other).
§Other hemostatic agents used for preprocedure prophylaxis, active bleeding, and recent bleeding included vitamin K (37%, 33%, and 30%, respectively), tranexamic acid (5%, 14%, and 0%, respectively), and recombinant activated factor VII (2%, 2%, and 0%, respectively).
Abbreviations: FFP, fresh frozen plasma; PCC, prothrombin complex concentrate.

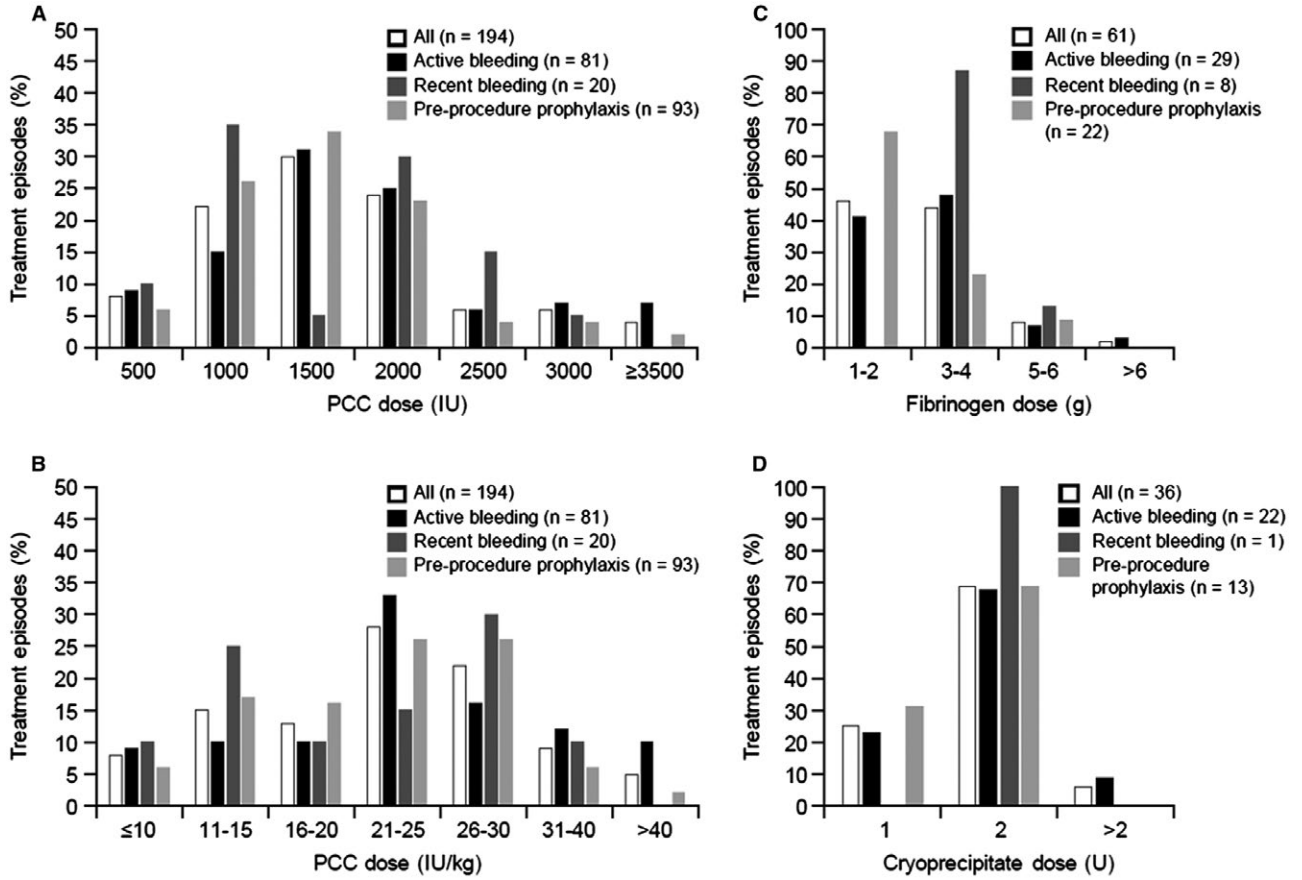

FIG. 1. PCC and fibrinogen dosing by episodes and clinical indication. (A) Absolute doses of PCC (IU). (B) PCC doses per unit body weight (IU/kg). (C) Doses of fibrinogen concentrate. (D) Doses of cryoprecipitate. Abbreviation: PCC, prothrombin complex concentrate.

of 3 to 4 g were given (44% of episodes; Fig. 1). The median dose of fibrinogen concentrate was 3.0 g (IQR: 2.0-3.0 g). Among patients receiving cryoprecipitate, the median dose was 2.0 units (IQR: 1.0-2.0 U).

PCCs AND COAGULATION TEST RESULTS BY EPISODE

Coagulation results were available within 7 hours before PCC administration in 71% of episodes and within 7 hours after PCC administration in 65% of episodes; in this group of patients with postadministration coagulation test results available, all dose ranges of PCC were included. No differences were found between patients receiving PCC for bleeding or prophylactically with respect to hemoglobin, PT, INR, activated partial thromboplastin time, or plasma fibrinogen levels, except for higher hemoglobin in patients treated prophylactically.

PCC therapy produced statistically significant reductions in PT and INR, regardless of the administration of fibrinogen concentrate/cryoprecipitate (Table 4). The percentage of patients with INR less than or equal to 1.5 increased significantly in response to PCC therapy. Nonsignificant trends toward shortened activated partial thromboplastin time values were observed. A significant increase in plasma fibrinogen was seen in patients who received fibrinogen concentrate or cryoprecipitate but not in patients who did not receive these products. No significant change in hemoglobin was observed in either of the two groups.

THROMBOSIS RISK FACTORS AND THROMBOTIC COMPLICATIONS—PATIENT-LEVEL ANALYSIS

Because thrombosis is a potential complication with the use of PCC, the prevalence of thrombotic

TABLE 4. COAGULATION RESULTS BEFORE AND AFTER PCC ADMINISTRATION

	No Fibrinogen or Cryoprecipitate				Concurrent Administration of Fibrinogen or Cryoprecipitate			
Variable	N	Pre-PCC Median (IQR)	Post-PCC Median (IQR)	*P* Value	N	Pre-PCC Median (IQR)	Post-PCC Median (IQR)	*P* Value
PT	46	27 (23, 34)	23 (20, 26)	< 0.001	43	30 (23, 54)	21 (18, 28)	< 0.001
INR	49	2.3 (1.9, 2.9)	1.8 (1.6, 2.1)	< 0.001	52	3.1 (2.0, 7.0)	1.9 (1.5, 2.8)	< 0.001
INR ≤ 1.5	49	6%	22%	0.005	52	4%	25%	< 0.001
aPTT	46	46 (38, 63)	45 (39, 56)	0.06	28	56 (45, 67)	46 (40, 66)	0.09
Fibrinogen	28	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)	0.37	22	1.0 (0.6, 1.4)	1.6 (1.1, 2.1)	< 0.001
Hemoglobin	39	8.4 (7.8, 8.8)	8.3 (7.9, 8.8)	0.75	31	8.1 (7.3, 9.3)	8.3 (7.2, 9.5)	0.36

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; IQR, interquartile range; PCC, prothrombin complex concentrate; PT, prothrombin time.

risk factors was assessed. Hypertension and diabetes were prevalent in 23% and 19% of patients, respectively. Eight percent of patients had previously undergone coronary artery bypass graft or coronary artery stenting or had a previous myocardial infarction; 4% had a previous transient ischemic attack/stroke; and 8% had other heart disease (e.g., atrial fibrillation, congestive cardiac failure). Four patients had previous deep vein thrombosis and pulmonary embolism, and 1 patient had Budd–Chiari syndrome. Portal vein thrombosis had occurred in 10 patients, and superior mesenteric vein thrombosis had previously affected 1 patient.

No cardiovascular adverse events or strokes were recorded during the 4-week follow-up period after administration of PCC. Three patients (3%) presented with venous thromboembolic events. The first patient was admitted for acute liver failure due to paracetamol overdose and underwent liver transplantation. A lack of blood flow in the hepatic artery following the transplant procedure was complicated by massive intra-abdominal bleeding, requiring further exploration, for which the patient was treated with PCC. Seven days after transplant, an angiogram revealed hepatic artery thrombosis, and a second transplant was required. The second patient was found to have a small, bilateral pulmonary embolism during a computed tomography scan of the chest, which was undertaken for another indication 15 days after PCC treatment. In the third patient, elective orthotopic liver transplantation was complicated by pericardial breach and massive transfusion; PCC was administered during the transplant procedure. One week after PCC treatment, the patient was found to have nonocclusive portal vein thrombosis.

MORTALITY

Forty-six patients died, giving an overall mortality rate of 44% (Supporting Table S3). None of the deaths were considered related to the administration of PCC. Of the 46 deaths, 11 (24%) occurred within 24 hours of the last PCC administration, and 33 (72%) occurred more than 24 hours after the last PCC treatment but before patients were discharged from the hospital. As expected, higher mortality rates were observed in patients admitted for decompensated liver disease and in those with Child-Pugh grade C.

Discussion

This large case series reports on the use of PCC to manage coagulopathy in patients with liver disease who have bleeding and are undergoing surgical procedures. Approximately three-quarters of patients who received PCC had chronic liver disease, and the remainder had acute liver failure. Similar numbers of patients received PCC treatment for preprocedure prophylaxis and for active or recent bleeding. PCC treatment was associated with a statistically significant correction of INR. Many patients with severe

coagulopathy had hypofibrinogenemia, necessitating fibrinogen supplementation in addition to PCC therapy. FFP use was lower when PCCs were used prophylactically, suggesting that PCC served as an FFP substitute; the need for concomitant platelet transfusion in one-third of treatment episodes reflects the severity of the underlying coagulopathy.

Reported use of hemostatic agents in patients with liver disease is often limited to case series and expert opinions. An early study in patients with liver disease showed that large volumes of FFP are required to produce a significant improvement in PT.[31] It was subsequently shown that the rise in coagulation factor levels following FFP therapy is variable; levels peaked at the end of treatment and returned to baseline at 24 hours.[32] Administration of higher doses of FFP (≥6 units) may increase its effectiveness, but such doses are rarely used and have been shown to bring PT to within 3 seconds of the normal range in only 20% of patients.[33]

Considering the limitations of FFP, our study expands on findings from smaller studies investigating PCCs to prevent or treat bleeding in patients with liver disease. In an early study of 22 patients requiring hemostatic treatment for bleeding or before an urgent surgical procedure, PCC (median dose of 25.7 IU/kg) was judged to have a "very good" clinical effect in 76% of the patients.[23] Markers of coagulation activation, including prothrombin fragment 1 + 2, thrombin–antithrombin complex, and D-dimers, were elevated after the administration of PCC, but no thromboembolic complications were reported.[23]

One large case series has described the use of PCC and/or fibrinogen in 156 patients (out of a cohort of 266) following liver transplantation; no significant difference was observed in thrombotic, thromboembolic, or ischemic adverse events between patients who received PCC and/or fibrinogen and those who did not.[34] An *ex vivo* study of PCC conducted using blood samples from liver transplant recipients showed that PCC was more effective than FFP in increasing thrombin generation.[25] Similarly, in a study testing the effects of *in vitro* addition of hemostatic agents using thrombin generation tests, FFP and rFVIIa only modestly increased thrombin generation in patients with compensated and acutely decompensated cirrhosis, whereas PCC increased thrombin generation 2-fold to 4-fold in these patients and approximately 2-fold in healthy individuals.[35] In a clinical study conducted across a range of settings, which included a small cohort of patients with liver disease, PCC therapy was associated with a trend toward a reduction in INR.[24] In a more recent study of 31 patients with liver disease, PCC was shown to achieve INR less than or equal to 1.5 in 6 patients (19%), whereas hemostasis was achieved in the same number.[26] These percentages were significantly lower than those seen in patients without liver disease (82% and 43%, respectively).[26] The investigators suggested this was a result of underdosing; however, this study reported a similar median dose to our study.

The contribution of coagulopathy to bleeding risk was recognized as early as the 1950s[36,37]; current guidelines consider bleeding risk and coagulopathy in their recommendations for management of patients with liver disease.[3,38] In a nationwide audit of percutaneous liver biopsy in England and Wales, bleeding risk with liver biopsy was approximately 3.3% with INR values of 1.3-1.5 but dramatically increased to 7.1% with INR greater than 1.5.[39] In our cohort of patients, we found a significant decrease in INR following PCC therapy, with INR less than or equal to 1.5 in a substantial proportion of patients (25% of patients with coadministration of fibrinogen or cryoprecipitate; 22% of patients with no coadministration; Table 4). However, INR was not decreased below 1.5 in all patients; this could be related to the relatively low doses of PCC and the fact that most samples for measuring INR were taken some time after PCC therapy. Among patients who received fibrinogen concentrate or cryoprecipitate in addition to PCC, a statistically significant increase in the plasma fibrinogen concentration was seen. An important advantage of using coagulation factor concentrates to treat coagulopathy is that the levels of specific coagulation factors can be increased reliably in a short time frame.

As with most treatments, dosing affects the safety profile of PCC. The median dose in our study was 22 IU/kg, which is below the lowest recommended dose for anticoagulation reversal (25 IU/kg).[17] It is also slightly lower than the median dose used in the study of PCCs in liver disease by Lorenz et al.[23] The safety outcomes in this study appear to support the relatively conservative dosing strategy currently used at our institute. However, further data are needed to confirm the optimum approach to PCC dosing in this setting.

Thromboembolic complications are an important consideration when using PCCs and particularly so

in patients with liver disease who are likely to have low levels of coagulation inhibitors. In the present study, thromboembolic complications occurred in 3% of patients, which was lower than expected for this patient population in the absence of PCC therapy. For example, in a review of orthotopic liver transplantation complications, portal vein thrombosis was reported to occur in 4.9%-10.6% of patients and deep vein thrombosis in 3.5%-8.6% of patients.[40] A review of rFVIIa studies reported an odds ratio for arterial thromboembolic events of 2.19 (95% confidence interval: 0.89-5.42) in patients with advanced liver disease.[41] Thus, our data suggest a more favorable safety profile with PCC than rFVIIa.

The high mortality rate reported in our study was considered not to be related to PCC therapy. Instead, high mortality may be more inherent to the multiple comorbidities associated with liver disease. This finding is consistent with a recent study comparing PCC use in patients with and without liver disease; mortality rate in patients with liver disease was 51.6% compared with 18.5% in patients without liver disease.[26]

Strengths of our study include the real-world setting and the large sample size given the clinical setting; we also believe the patients at our center are typical of a UK tertiary center with a liver transplant unit. This means the findings should be applicable to clinical practice. Although it is possible that there was a selection bias regarding the use of PCCs (i.e., patients with more severe coagulopathy are selected for PCC therapy), such bias may be expected in clinical practice, reinforcing the applicability of our results to everyday practice.

Limitations of our study include the retrospective study design with no control groups; this prevented any comparison against patients who did not receive PCC. There was also substantial heterogeneity across the patients in the study. Because bleeding sites and urgency of reversal varied between patients, hemostatic interventions were multifactorial; therefore, there was no objective clinical assessment. Moreover, more than half of the study population received PCC for prophylaxis; however, the benefits of prophylactic correction in this population are not clear. It should also be noted that other hemostatic agents were used in addition to PCC for a large proportion of patients in our study, which may not be representative of practices at other centers and limits interpretation of the data in terms of PCC use.

Although a significant effect on INR was observed in our study, INR was reported only for 65% of episodes. Furthermore, the clinical significance of this finding is unclear given recent findings suggesting "rebalanced hemostasis" in patients with liver disease in which both procoagulants and anticoagulants are reduced.[42] This rebalancing means that, despite PT prolongation, thrombin generation may in fact be normal, as demonstrated in thrombin generation assays.[11,42] Conventional coagulation tests, including PT and INR, measure levels of procoagulants but not levels of anticoagulants; as a consequence, PT and INR are not reliable indicators of overall coagulation status in patients with liver disease, with the threshold values for increased risk of thrombosis and bleeding poorly defined. Global assays, such as the thrombin generation assay, evaluate the overall balance of coagulation factors[43]; however, the physiological relevance of the modified assay with regard to bleeding tendency has not been demonstrated in studies of invasive procedures or animal models. Furthermore, the assay has not been validated for prediction of bleeding risk and is not routinely available to guide hemostatic treatment. Despite their limitations, in the absence of a validated global assay, clinical decisions are still made based on conventional PT and INR testing.[43]

Future studies of PCC for this patient population need to be prospective and include a comparator group, objective measures of hemostasis (e.g., blood loss), and comprehensive evaluation of coagulation. In addition, the use of additional hemostatic therapy could be assessed—preferably with a coagulation management algorithm to ensure consistency.

In conclusion, our study showed that PCCs were used more frequently in patients with chronic liver disease than those with acute liver failure. Similar numbers of patients received PCC treatment for preprocedure prophylaxis and active/recent bleeding. PCC therapy was effective in improving coagulation test results, with no evidence of an increased risk of thromboembolism. These findings highlight the need for further assessment of the potential role for PCC as hemostatic therapy in patients with liver disease.

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