mean levels of AP activity in PCT-FFP from Site B (78 ± 4 IU/dL) and Site L (76 ± 4 IU/dL) were slightly outside the lower limit (80 IU/dL) of the reference range.

After PCT, the mean retention of antithrombotic proteins ranged from 84 to 90 percent for PC and 82 to 85 percent for AP (Tables 2 and 3). No differences were observed between apheresis and whole blood–derived plasma. Similarly, the mean retention in PCT-FFP ranged from 95 to 100 percent for PC and 95 to 96 percent for AT (Tables 2 and 3). The results were comparable between apheresis and whole blood–derived plasma.

To compare the processing characteristics between apheresis plasma (n = 90) and whole blood–derived plasma (n = 96), the results from all three sites were combined for analysis (Table 4). There were no significant differences in the activity of PC of either C-FFP or PCT-FFP between apheresis and whole blood–derived plasma. Whole blood–derived plasma contained significantly higher levels of PS before and after PCT than apheresis plasma (see Table 4). In contrast, the levels of AT and AP were generally lower in whole blood–derived plasma compared to apheresis plasma and reached significance (see Table 4).

The overall (n = 186) mean activities of the antithrombotic proteins in C-FFP and PCT-FFP were within the reference ranges. After PCT, mean retention of PC and AP was 86 and 83 percent, respectively, whereas mean retention of PS and AT was 97 and 96 percent (Table 4).

DISCUSSION

The PCT process for preparation of pathogen-inactivated FFP involves the addition of amotosalen to a nominal concentration of 150 µmol per L (range, 110-225 µmol/L), illumination of the plasma mixture with a 3 J per cm² UVA treatment, and removal of residual amotosalen to less than 2.0 µmol per L by a flow CAD. Three European centers participated in this study to validate the process under routine blood bank operation conditions. Each center processed 30 units of apheresis plasma and 30 to 36 units of whole blood–derived plasma with integral disposable sets that have received CE Mark approval and commercial UVA illuminator. The PCT process was completed within the time frame for FFP, allowing units to be frozen within 8 hours of collection.

The mean pretreatment amotosalen concentration from all three sites was 143 ± 8 µmol per L (n = 186), which is well within the target system performance range of 110 to 225 µmol per L. The use of the microprocessor-controlled UVA illuminator ensured delivery of the UVA treatment dose of 3 J per cm². All three centers demonstrated the addition of the correct amotosalen concentration, combined with a 3 J per cm² UVA treatment dose, thus ensuring robust pathogen inactivation. The mean amotosalen level after the CAD treatment for all centers was 0.6 ± 0.1 µmol per L (n = 186), which is significantly below the target performance value of 2.0 µmol per L. The mean residual amotosalen levels among the three sites ranged from 0.5 ± 0.1 to 0.7 ± 0.1 µmol per L with no units having residual amotosalen higher than 1.2 µmol per L, demonstrating the consistency and the efficacy of the CAD. These results demonstrate that the PCT process can be performed consistently under blood bank conditions.

The quality of PCT-FFP was assessed for activity of FVIII with respect to meeting national and European regulatory guidelines.[8] The consistency of the PCT process was assessed by the retention of all factor activities in PCT-FFP compared to levels in pretreatment plasma samples.

The factor most affected by PCT was FVIII with a mean of 26 percent reduction in activity. However, residual activity is within the current requirement for FFP as the level of FVIII is greater than 50 IU per dL in the European Pharmacopoeia standard for therapeutic FFP.[9] The mean FVIII activity after PCT was 107 ± 35 IU per dL (n = 90) for apheresis plasma and 88 ± 18 IU per dL (n = 96) for whole blood–derived plasma or an overall mean of 97 ± 29 IU per dL (n = 186). All units had FVIII activity greater than 50 IU per dL. In France, greater than 90 percent of quality control samples must have greater than 70 IU per dL in FVIII. Preliminary studies measuring the thrombin generation time for PCT-FFP have shown no difference from untreated plasma for peak thrombin levels, lag time to start of thrombin generation, or total thrombin produced.[10] These observations suggest that the reduction in FVIII levels are not critical to generation of thrombin and the ultimate conversion of fibrinogen to fibrin. These observations of normal thrombin generation are in contrast to those recently reported for plasma prepared with methylene blue and visible light.[11]

Fibrinogen was also affected by PCT with a mean of 26 percent reduction in the clottable fibrinogen levels. Although there is no required standard for the level of fibrinogen in FFP, the mean levels retained in PCT-FFP (217 ± 43 mg/dL, n = 186) were within the reference range. Prior clinical studies with PCT-FFP for support of liver transplant with massive transfusion have shown no increased requirement for plasma or cryoprecipitate, indicating that the levels of fibrinogen in PCT-FFP are sufficient.[4] These patients have a significant period of fibrinolytic activity after unclamping of the transplanted liver. The study examined the use of conventional FFP, cryoprecipitate, and PCT-FFP for support of these patients and observed no differences to indicate that the reduced levels of fibrinogen in PCT-FFP were clinically relevant. In addition, the levels of AP activity are reasonably conserved in PCT-FFP.[1] Although the levels of fibrinogen are reduced by the treatment, the levels appear adequate to support hemostasis in patients with active fibrinolysis.

Other coagulation factors (FII, FV, FVII, F IX, FX, FXI, FXIII) were less affected by PCT. The mean factor activities in PCT-FFP were within the reference ranges. Retention of activity after PCT ranged from 81 to 97 percent. Of specific importance were the levels of FVII, which is the factor with the shortest half-life and thus the most critical for transfusion support of acquired complex coagulopathy. In addition, levels of the anticoagulant PC and PS and AT were relatively unaffected by PCT and α2-AP was well conserved.

There was slight prolongation in PT and aPTT. PCT-FFP, however, retained PT and aPTT within the reference range. The slight changes in PT and aPTT after PCT were not associated with any adverse clinical observations in controlled clinical trial settings, and treatment of congenital coagulation defects has demonstrated consistent correction of both the PT and aPTT after transfusion with PCT-FFP.[3-5,12]

The results of this study demonstrate that there is good retention of relevant coagulation factor activities and antithrombotic protein function in PCT-FFP from either apheresis or whole blood and that these products meet the requirements for therapeutic plasma. In a separate study, the effect of storage on FI, FII, FV, FVII, FVIII, F IX, FX, and FXI has been evaluated.[13] The results show that therapeutic levels of these factors were conserved in PCT-FFP after 12 months of storage at –18°C and after 18 months of storage at –25°C. Similar results were obtained in storage studies conducted at one of the three centers (Site S, data not shown) with PCT-FFP prepared from apheresis plasma frozen up to 1 year. In addition, clinical trials with PCT-FFP have shown that this product is sufficient for therapeutic support of patients with each of the major clinical indications for plasma transfusion.

The effect of PCT on plasminogen and von Willebrand factor (VWF) has also been evaluated.[14,15] After treatment, plasminogen was within normal ranges and retained 94 percent. The von Willebrand antigen, VWF:ristocetin cofactor, components of the von Willebrand complex, including multimers and VWF:CP activity, remained within normal ranges and demonstrated greater than 98 percent retention. Because of the stability of these factors after treatment, they were not included in the current validation study.

When the results were compared between sites or between types of plasma, significant differences were observed, although the differences were small, not likely of clinical relevance, and did not appear to follow a specific pattern. The observed differences could simply be due to the geographic variation in the plasma characteristics and the slight variation in the processing techniques. Of particular interest is that the FVIII activities as well as the retention for apheresis PCT-FFP in Site B were significantly higher than the values obtained in the other two sites. This difference could not be completely explained by the different apheresis collection platforms. Site S used the Haemonetics platform, but the same Baxter platform was used in both Site B and Site L. The observed difference between Site B and Site L was most likely due to the variation in donor population and processing techniques. Different anticoagulants may introduce variability but were poorly defined and not well evaluated. Overall, PCT-FFP manufactured in the three different geographic locations were of comparable quality. All met the respective national and European standards for transfusable FFP.

Previous studies with cryoprecipitate prepared from photochemically treated plasma yielded approximately 95 and 88 percent retention of fibrinogen and FVIII, respectively, compared to cryoprecipitate prepared from untreated plasma.[16] Cryosupernatant prepared from photochemically treated plasma retained adequate levels of critical plasma proteins for plasma exchange therapy in acute thrombocytopenic purpura. These data indicate good preservation of hemostasis control proteins such as PS, α2-AP, and VWF-cleaving protease activity.[17]

In summary, the results of process validation studies from three European centers demonstrated the consistency of the PCT process for FFP. From a blood center perspective, scaleup manufacturing of PCT-FFP in routine is feasible by the ability to treat individual large-volume units of fresh apheresis plasma and small pools of whole blood–derived plasma. The mixture of whole blood plasma from two or three matched donations is similar to the procedure for whole blood–derived PLT components. Since adult patients will require 4 to 6 FFP units (200 mL each) for a therapeutic episode, donor exposures are consistent with current practice in which whole blood plasma units are processed individually. A similar PCT system utilizing amotosalen and UVA light for PLT components has been in routine use in some blood centers in European countries.[18] Both PLT and plasma components are treated with the same UVA illumination device thus simplifying the logistics of implementation of two pathogen inactivation systems in one blood center.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2008. 5. 26	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	Blue DE, Cruz J, Limiac A, Spinola S, Davis TE, Waxman D, McCarthy L, Smith D. American Society for Microbiology 108th General Meeting; 2008 Jun 1-5; Boston.	公表国 米国
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社)			

研究報告の概要

○輸血による*Babesia.microti*死亡例
輸血によって*Babesia microti*に感染し死亡する例は赤血球を含む輸血100万単位あたり1件未満と見積もられている。疾患は通常無症候性だが、無脾症、高齢、免疫抑制状態の患者では感染によって死に至ることがある。
症例:腎臓疾患で透析を必要としていた61歳の女性患者。入院45日前に赤血球2単位を輸血され、その後更に2単位追加輸血された。入院前日、吐き気と発熱を訴えたため、血液培養をオーダーし、抗生物質が投与された。リハビリ施設に戻る際に、体温は39.4℃を示し、低血圧で、昇圧剤を必要とし、敗血症の症状を呈した。血液塗抹標本では、赤血球の5~15%にトロフォゾイト(栄養体)があり、*Plasmodium falciparum*か*B. microti*と考えられた。静注キニジン及びクリンダマイシン投与が開始された。赤血球交換により寄生虫血症は1%まで低下した。投薬は適切だったが、播種性血管内凝固症候群(DIC)を発症し6日後に死亡した。外出や旅行はしていなかったため、唯一のリスクファクターは輸血と考えられた。
結果:*Babesia*はCDCで形態学的に確認された。患者の入院時の検体では6%の寄生虫血症と*B. microti* PCR陽性が認められた。輸血された製剤の供血者4名のうち1名がIFAで*B. microti*陽性となった。供血者はダニに噛まれた記憶はなく、流行地域に旅行したこともなかった。
結論:上の臨床症状と転帰は*Babesia*の輸血伝播による死亡例の中では珍しいものではないが、中西部で発生したという点が他と異なっている。ベクターIxodes scapularisが寄生する中西部のオジロジカの頭数増加に伴い、供血者における*Babesia microti*抗体陽性率を解明する為の研究を行うべきである。

報告企業の意見	今後の対応
輸血によると考えられる*Babesia microti*に感染し死亡した症例の報告である。	今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

Abstract Title: Fatal Transfusion-Transmitted *Babesia microti*

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Background: Fatal transfusion-transmitted *B. microti* has an estimated incidence of <1:1,000,000 per unit of transfused red cell containing blood products. The disease is usually asymptomatic; however, fatal infections occur in asplenic, elderly or immunosuppressed individuals. **Case Report:** The 61-year-old female patient had renal disease requiring dialysis. Forty-five days prior to admission she received two units of packed red cells and then two more. One day prior to admission, the patient complained of nausea and fever. Blood cultures were ordered and antibiotics administered. Upon returning to the rehabilitation facility, she spiked temperatures to 103°F and was admitted to the hospital. She was hypotensive, requiring vasopressor support, and appeared to be septic. The blood smear revealed trophozoites in 5 to 15% of red cells, probable species: *Plasmodium falciparum* vs. *B. microti.* Treatment with intravenous quinidine and clindamycin was begun. A red cell exchange reduced parasitemia to 1%. Despite appropriate medication, the patient developed disseminated intravascular coagulation and expired 6 days later. Since she was confined indoors and did not travel, the only risk factor was transfusion. **Results:** *Babesia* was confirmed morphologically by CDC with 6% parasitemia and PCR positivity for *B. microti* from the patient's specimen at admission. The three donors available for testing were negative for *B. microti* and all samples were negative for *P. falciparum* by PCR. One blood donor and the patient were positive for *B. microti* by immunofluorescent antibody (IFA). The seropositive donor had no recollection of a tick bite and did not travel to endemic areas. **Conclusion:** The above clinical presentation and course is not atypical for rare fatal cases of transfusion-transmitted *Babesia*. This is an unusual case as it arose in the Midwest. With the expanding Midwest white-tailed deer populations harboring the vector, *Ixodes scapularis*, studies to determine the regional incidence of *Babesia microti* seropositive blood donors may be warranted.

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医薬品 研究報告 調査報告書

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一般的名称	人赤血球濃厚液	研究報告の公表状況	飯岡大, 前追善智, 中村文彦, 林孝昌, 津田勝代. 第56回日本輸血・細胞治療学会総会; 2008 Apr 25-27; 福岡.	公表国
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研究報告の概要

○血小板濃厚液の輸血後に、急性呼吸不全と*Bacillus cereus*(*B. cereus*)による髄膜炎を併発した症例

【緒言】輸血後細菌感染症は、診断・治療に難渋し、時に致命的な状態になることもある。我々は、*B. cereus*の輸血後感染症で急性呼吸不全および重症髄膜炎を併発した症例を経験し、その治療および診断経過が今後の対策につき有用と考えられここに報告する。

【症例】76歳女性。64歳に再生不良性貧血と診断、免疫抑制療法に不応で、71歳よりは赤血球および血小板輸血が定期的に必要となった。平成19年4月、血小板輸血を施行中、発熱・悪寒、その後急速な呼吸不全を認め、胸部X線・心エコー検査より、輸血関連肺障害(TRALI)と判断した。メチルプレドニゾロン500mg投与で呼吸状態は改善し発熱も消退した。しかし発症12時間後、嘔気・頭痛の出現と共に再び発熱を認めた。感染症を考え直ちに抗生剤を開始したが悪化し、発症16時間後には右方への眼球偏位と意識障害(昏睡)が出現した。髄液検査にて細胞数・蛋白の増加を認め、脳波でも異常波を認めたことから、細菌性髄膜炎および症候性てんかんと診断した。その後、抗生剤および抗てんかん薬が奏効し、発症第13日には意識清明となり、発症第25日には後遺障害なく退院できた。輸血関連感染の診断目的に当院で各種培養検査を施行したところ、血小板残液の鏡検・培養検査で*B. cereus*が検出された。髄液では、初回抗生剤投与後に採取した影響もあり鏡検・培養検査は陰性であったが、遺伝子検査PCR法にて、血小板製剤と同一菌株の*B. cereus*が検出され、今症例が輸血後感染症から髄膜炎に進展したと考えられた。一方で、凍結処理された供血者保存血漿では、培養検査・遺伝子検査共に陰性であった。

【考察】TRALI様の急性呼吸不全を呈した際は、輸血後感染症も視野に入れた対応が必要である。髄膜炎併発例の報告はこれまでに無いが、輸血後感染症治療では髄液移行性も考慮した抗生剤選択が求められる。培養検査だけでなく、遺伝子検査まで施行することが、診断及び同一菌株の証明に重要である。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

自発報告:2007年5月28日付1-07000033

報告企業の意見	今後の対応
血小板濃厚液の輸血後に、TRALI様の急性呼吸不全と髄膜炎を併発し、血小板残液から*Bacillus cereus*が検出された症例の報告である。 本症例について、日本赤十字社では抗白血球抗体、抗顆粒球抗体検査を実施し、臨床経過及び診断基準よりTRALIであると評価した。患者の血液培養が陰性で、当該血小板製剤と同一採血時の凍結血漿では無菌試験陰性であったことから、輸血による細菌感染があったかどうかは不明である。	日本赤十字社では、輸血による細菌感染予防対策として平成18年10月より血小板製剤について、また、平成19年3月より全血採血由来製剤について、初流血除去を導入した。また、全ての輸血用血液製剤について、平成19年1月より保存前白血球除去を実施している。さらに、輸血情報リーフレット等により細菌感染やウイルス感染について医療機関へ情報提供し注意喚起しているほか、細菌感染が疑われる場合の対応を周知している。今後も細菌やウイルスの検出や不活化する方策について情報の収集に努める。