A General Change of the Platelet Transfusion Policy from Apheresis Platelet Concentrates to Pooled Platelet Concentrates is Associated with a Sharp Increase in Donor Exposure and Infection Rates

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Key Words

Donor exposure · Apheresis platelet concentrates · Pooled platelet concentrates · Infection rates from apheresis platelet concentrates · Infection rates from pooled platelet concentrates

Summary

Background: We compare the actual with the potential donor exposure and possible infection rates in the Hanover Medical School (MHH) platelet (PLT) transfusion recipients if the current MHH standard of apheresis PLT concentrate (A-PC) supply would be replaced by a pooled PLT concentrate (P-PC) transfusion regimen. **Donors, Patients, and Methods:** The electronic records of the MHH Institute of Transfusion Medicine and the MHH Department of Medical Controlling were evaluated to assess the development of PLT needs and supply at MHH from 2003–2006. For 2006, we evaluated all PLT transfusion recipients with respect to their overall transfusion needs, classified them for low and high PLT transfusion needs, and related them to the diagnostic groups that underlie their PLT demands. We assumed a P-PC preparation procedure using 4 whole blood-derived buffy coats for all calculations for potential donor exposure. To predict the possible infection rates of an unrecognized viral infection with low prevalence in the general population to A-PC or to P-PC recipients and the influence of neutralizing agent specific antibodies (NAB), we established a mathematical contamination/infection model based on the current PLT transfusion mode and data about GBV-C virus infection among Hanover blood donors. **Results:** From 2003 to 2006, the 1,300–1,400 persons comprising MHH apheresis donor pool covered a 36% increase in PC transfusions. The exclusive use of P-PCs instead of A-PC would require a total of 36,240–49,276 whole blood donations to meet MHH demands, corresponding to a more than 1 log step increase in donor exposure. For individual hematological patients, the change to P-PCs would imply an 80–125%, for individual surgical patients a 40–50% higher donor exposure. Our infection model revealed an approximately 4 times higher infection. **Conclusions:** A change to P-PC would imply a more than one log step higher donor exposure, and an unrecognized infection with a prevalence around 1% leads to an up to 4 times higher infection rate. A general change in the PC transfusion policy that favors P-PCs is dangerous and must be avoided.

Schlüsselwörter

Spendereexposition · Thrombozytapheresekonzentrate · Thrombozyten-Pool-Konzentrate · Infektionsraten bei Anwendung von Thrombozytapheresekonzentrat · Infektionsraten bei Anwendung von Pool-Thrombozytenkonzentrat

Zusammenfassung

Hintergrund: Ziel der Studie war die Erfassung der tatsächlichen im Vergleich zur potentiellen Spendereexposition sowie der möglichen Infektionsraten bei Empfängern von Thrombozytenkonzentrat (TK), falls der gegenwärtige Transfusionsstandard an der Medizinischen Hochschule Hannover (MHH) – die Patientenversorgung mit Apheresekonzentrat (A-TK) – von einer Transfusionsstrategie mit gepoolten Thrombozytenkonzentrat (P-TK) abgelöst würde. **Spende, Patienten und Methoden:** Wir haben die elektronischen Datenbanken des MHH-Instituts für Transfusionsmedizin sowie der MHH-Abteilung für Medizinkontrolling bezüglich der Entwicklung des Thrombozytenbedarfs und der Thrombozytenversorgung für die Jahre 2003–2006 ausgewertet. Bezogen auf das Jahr 2006 wurden alle MHH-Thrombozytenempfänger hinsichtlich des Gesamttransfusionsbedarfs, niedrigen bzw. hohen Thrombozytenbedarfs bzw. auf die dem Thrombozytenbedarf zugrunde liegenden Erkrankungen untersucht. Auf der Basis von 4 Buffy Coats aus Vollblutkonserven als Ausgangsmaterial für die Herstellung eines P-TK berechneten wir die potentielle Spendereexposition für die MHH-TK-Empfänger. Wir entwickelten ein mathematisches Modell, um mögliche Infektionsraten bei einer unerkannten viralen Infektion mit niedriger Prävalenz in der Allgemeinbevölkerung bei A-TK- oder bei P-TK-Empfängern unter Einschluss neutralisierender virusspezifischer Antikörper vorherzusagen. Dieses Modell basiert auf der gegenwärtigen Transfusionspraxis für TK in Hannover und bekannten Daten zu GBV-C-Virusinfektionen bei Hannoveraner Blutspendern. **Ergebnisse:** Der 1,300–1,400 Personen umfassende MHH-Apheresespenderpool stellte für die Jahre 2003 bis 2006 sicher, dass der 36%ige Anstieg der Thrombozytentransfusionen bewältigt werden konnte. Die abschließliche Anwendung von P-TK anstelle von A-TK hätte 36.240–49.276 Vollblutspender erfordert, was einem Anstieg der Spendereexposition um mehr als eine Logstufe entsprachen hätte. Individuelle Thrombozytenempfänger mit niedrigem, moderatem, hohem und sehr hohem A-TK-Bedarf hätten eine um 42, 67, 84 und 109% höhere Spendereexposition gehabt. Für individuelle hämatologische Patienten hätte der Wechsel des Transfusionsregimes zu P-TK eine um 80–125%, für individuelle chirurgische Patienten eine um 40–50% höhere Spendereexposition zur Folge gehabt. Unser Rechenmodell zur Abschätzung von Infektionsfolgen zeigt eine zirka viermal höhere Infektionsrate. **Schlussfolgerungen:** Ein Wechsel der Transfusionsstrategie auf Pool-TK würde mit einer um mehr als eine Log-Stufe erhöhten Spendereexposition einhergehen, und eine unerkannte Infektion mit einer Prävalenz von zirka 1% führt zu einer um den Faktor 4 erhöhten Infektionsrate bei Pool-TK-Empfängern. Ein genereller Wechsel in der Transfusionsstrategie für Thrombozytenkonzentrate ist daher als gefährlich anzusehen und muss unbedingt vermieden werden.

Introduction

Single donor (SD) blood components have long been regarded as a gold standard in transfusion medicine because they were associated with lower risks for transmission of viral or bacterial infections to transfusion recipients than pooled blood components. This was true in the recent past as demonstrated by a report that presented results from a 1998 through 2001 survey in Germany with bacterial contamination rates of 0.60% for pooled platelet concentrates (P-PCs) prepared from 4 whole blood-derived buffy coats (BC) versus 0.18% for apheresis-derived SD PCs (A-PCs) [1]. However, a number of technical developments as well as recent scientific findings are currently undermining the preference of SD A-PC components. Different pathogen reduction or inactivation techniques that are applicable to platelets (PLT) such as the Intercept™ system (Cerus Europe BV, Leusden, The Netherlands; based on the application of amotosalen HCl plus ultraviolet A light) have entered the market [2], have gained regulatory clearance and are clinically used [3] or can be foreseen to invade clinical medicine in the near future (Mirasol™, Navigant Biotechnologies Inc., Zaventem, Belgium; based on the application of riboflavin plus UV light at 285–365 nm [4]). The increased sensitivity of nucleic acid amplification testing (NAT) has considerably reduced the ‘window period’ between the infection of the donor and the moment at which screening tests are capable of detecting the infectious agent. This was especially proven for classical transfusion transmitted infections (TTI) such as HIV-1 and HCV, thereby reducing the residual TTI risk to extremely low values in the range below $1:10^6$ for HIV-1 and of $1:10^6$ – $1:10^7$ for HCV per year [5, 6]. Moreover, a very recently published prospective multicenter study from different German Red Cross blood donation services has shown that the rate of confirmed-positive bacterially contaminated PCs (mostly *Propionibacterium acnes* or *Staphylococcus epidermidis*) did not differ significantly between A-PCs (0.09%; 1/1,169) and P-PCs (0.06%; 1/1,544) [7]. For years, there have been intense controversies regarding in vitro quality parameters and storage lesions in both A-PCs and P-PCs products. Boeck and Heim [8] have observed a much better in vitro hemostatic capacity of A-PCs over P-PCs when aggregation experiments are performed and closure times of the PFA 100 system are measured. They supposed a lower level of cellular activation in A-PCs to be causative for these differences. When other parameters were investigated, such as P-selectin (CD62p) on the platelet surface or extracellular, CD63, CD41 (glycoprotein IIb/IIIa), or CD42b (glycoprotein Ib alpha), the opposite turned out [9, 10]. These predominantly flow cytometric analyses showed a higher activation level in A-PCs, especially on day 1, with a tendency to converge to the level of P-PCs at the end of storage (days 5–7). In view of these conflicting laboratory results, clinical parameters could help to answer the question of the most appropriate product selection. Interestingly, there are a number

of studies that describe a significantly better corrected count increment (CCI) in A-PC recipients regardless of A-PCs were compared to P-PCs prepared by the PRP method or by the BC method that is more common in Europe [11–13]. Consistent to this finding were longer transfusion intervals [13] and lower rates of patients refractory to further platelet transfusions [12]. However, these findings did not always translate into clinical advantages such as lower numbers of severe bleeding complications or death due to uncontrollable bleeding [11, 13]. Thus, it cannot surprise that the value of SD A-PCs has been questioned [14, 15]. Accelerated pressures of health care reform have also created an environment in which considerations of cost effectiveness begin to superimpose issues of patient care [15]. To date, in European countries like Denmark, Finland, and the Netherlands, A-PCs have already been replaced to a degree of 88% or more by P-PCs [16]. In Germany, a group of specialists in transfusion medicine, hematology and hemostaseology have raised a lively discussion about PC product selection. They classified A-PC and P-PC, prepared by the BC method, to be equal with respect to transfusion success and transfusion complications, and recommended that the product choice should be based on local ‘availability only’ [17, 18].

In this context, it is a remarkable finding that the increasing donor exposure that goes inevitably along with P-PC usage is a well accepted but hardly investigated parameter. The elevated donor exposure (4–6 times higher for P-PCs than for A-PCs) is often mentioned as a significant disadvantage of P-PC [2, 4, 7, 14, 16, 19–22], but exact calculations about the magnitude of the increase in donor exposure are rare. We are aware of only one such calculation from the early 1990s: In an attempt to estimate the cost effectiveness of A-PC compared to P-PCs, Lopez-Plaza et al. [15] assessed a 3–4 times higher donor exposure in small cohorts of cancer (breast cancer, $n = 54$) and hematological patients (acute myelogenous leukemia, $n = 47$; chronic myelogenous leukemia, $n = 35$; non-Hodgkin’s lymphoma, $n = 40$) and a 1.5–2 times higher donor exposure in coronary artery bypass grafting patients (CABG, $n = 77$) with the exclusive use of P-PCs. The calculations related on the assumption of 7 donors per P-PC transfusion episode. As breast cancer today is no longer treated by autologous stem cell support, the intensity of treatment regimen for hematological malignancies has increased, and the number of donors per BC-derived P-PC today is lower (usually not exceeding 4–6 donors), the donor exposure assessments of Lopez Plaza et al. [15] need re-evaluation. Based on the large PLT transfusion data pool of our institution, we here present careful calculations of nowadays donor exposure for individual patient groups as well as for the entire group of the Hanover Medical School (MHH) PLT transfusion recipients. These calculations reflect the possible consequences that would be associated with a general change of the transfusion policy from A-PCs to P-PCs.

Table 1. MHH-PC transfusion recipients 2003–2006, calculated donor exposure P-PC vs. A-PC

Year	Total PC-Tx-Rec	A-Donors	Aphereses	Apheresis / donor / year	A-D/Rec ratio, x-fold	MHH PC-Tx			P-(WB) donors ^a	P-D/Rec ratio, x-fold	P-D vs. A-D ratio, x-fold
						inpatient	out-patient	total			
2003	1,308	1,387	4,951	3.6	1.06	8,325	735	9,060	36,240	27.7	26.1
2004	1,582	1,489	4,405	2.8	0.94	8,946	568	9,514	38,056	24.1	25.6
2005	1,725	1,434	4,749	3.3	0.83	9,828	763	10,591	42,364	24.6	29.6
2006	1,774	1,392	5,525	4	0.79	11,634	685	12,319	49,276	27.8	35.2

^aBased on the least number for P-PC (4 BC/P-PC).

PC-Tx-Rec = Platelet concentrate transfusion recipients; A-D/Rec ratio = apheresis donor to PC recipient ratio; P-D/Rec ratio = pool donor to PC recipient ratio; P-D vs. A-D ratio = pool donor versus apheresis donor ratio.

Table 2. Calculation of GBV-C contaminations among MHH PC recipients with respect to the MHH 2006 PC transfusion needs, comparison of A-PC versus P-PC

Apheresis PCs		Pooled PCs	
MHH needs 2006 A-PC, n	12,319	P-PC, n	12,319
A-PC donors, n	1,392	P-PC donors, n	49,276
A-PC aphereses, n	5,525		
Apheresis/donor, n	4		
PC (split products)/donor, n	2.23		
Donors GBV-C-positive (1.2%), n	17	donors GBV-C-positive (1.2%), n	591
Calculation GBV-C contamination, n	$17 \times 2.23 \times 4$	calculation GBV-C contamination, n	$49,276 \times 0.012$
Calculated contaminated A-PC, n	152	calculated contaminated P-PC, NAB frequency 0%, n	591
Calculated contaminated A-PC, NAB frequency 10%, n	n. a.	calculated ^a contaminated P-PC, NAB frequency 10%, n	424 ^b
Calculated contaminated A-PC, NAB frequency 20%, n	n. a.	calculated ^a contaminated P-PC, NAB frequency 20%, n	298 ^b
Calculated contaminated A-PC, NAB frequency 30%, n	n. a.	calculated ^a contaminated P-PC, NAB frequency 30%, n	200 ^b

^aFormula see Donors, Patients, and Methods.

^b3.43, 2.42, and 1.62% of 12,319 P-PC.

n.a. = Not applicable.

Donors, Patients, and Methods

MHH is a German university clinic operating a large variety of 26 different clinical departments. In 2006, 1,011 beds (excluding psychiatric beds) with an average utilization of 82.2% were run for treatment of 34,537 individual inpatients [23]. MHH has by far the highest casemix index in Germany (1.75 in 2006 [23]). The clinical departments with large needs for PLT products include Adult Hematology/Oncology, Pediatric Hematology/Oncology, Cardiac Surgery, Trauma Surgery, and others. To meet these demands, MHH has an independent Institute for Transfusion Medicine that operates a blood donation service with a large apheresis unit. From 2003 to 2006, the apheresis unit performed 5,034, 4,404, 4,848, and 5,525 PLT aphereses, covering completely the MHH PLT demand by A-PC products. The temporary decline of the PLT aphereses from 2004 to 2005 was due to the implementation of triple PLT apheresis in January 2004. The MHH PLT apheresis (split) products contain an average of $2.8 \pm 0.30 \times 10^{11}$ PLT/therapeutic unit (TU) [24].

The clinical focus of MHH is hematopoietic stem cell and solid organ transplantation. In 2006, 28 (22 adult, 6 pediatric) beds for hematopoietic stem cell transplantation were run. In total, 132 hematopoietic transplants and 486 solid organ transplants were performed [23]. Our evaluation included the time period from 2003 to 2006 to demonstrate overall trends such as the development of PLT production at MHH, development of PLT support, and PLT transfusion recipients. In a second step, all MHH

PLT transfusion recipients of 2006 were evaluated with respect to their overall transfusion needs, were classified as recipients with low and high PLT transfusion needs and were related to the main diagnostic groups that underlie their PLT demands. All calculations were performed to determine their actual donor exposure in comparison to their potential donor exposure if the current MHH standard of the exclusive use of A-PC would be completely replaced by P-PCs prepared from 4 BCs. As the MHH numbers of HLA-matched PLT transfusions were low (3.23 and 3.38% for 2005 and 2006), these figures were neglected. For determination of donor exposure, the evaluation was limited to labile blood components only (red cells, PLT, fresh frozen plasma, and in rare instances neutrophil concentrates). To assess the transfusions that had actually taken place, the electronic transfusion records of the MHH Institute for Transfusion Medicine data base was evaluated. To assess the main patient groups (e.g. hematological vs. surgical patients) that were associated with PLT transfusion needs, the electronic data base of the MHH Department of Medical Controlling could be additionally used.

To predict the possible rates of transmission of an unrecognized viral infection with a low prevalence in the general population to A-PC or to P-PC recipients, we established a model that was based on the current platelet transfusion mode in Hanover and known data about the GBV-C virus or carriers of neutralizing antibodies to GBV-C in Hanover. GBV-C is a well known flavivirus that was first isolated in the mid 1990s from the blood of patients with unclear non-A-E hepatitis [25, 26]. Because of this

way of detection and the early finding of its transmissibility via transfusion, the virus quickly became a candidate as causative agent for non-A-C posttransfusion hepatitis and was tentatively named hepatitis G virus [27]. A GBV-C prevalence of 1-4% was noted among blood donors in the US and Europe [27, 28]. The published figures for German blood donors [29-33] and other apparently healthy individuals (e.g. medical professionals [30]) with a GBV-C prevalence of 1.34-1.6% (for the metropolitan area around Frankfurt/Main [29]), 1.8% for Berlin [30], and 0.8% from a small donor cohort (n = 120) in Hanover [33]) suggest a similar prevalence range. An unpublished investigation including a larger Hanover blood donor group revealed a prevalence of 1.2% (6/500 donors). Neutralizing antibodies (NAB) against GBV-C (e.g. anti-E2) that usually indicate a resolved GBV-C infection range from 3-14% for blood donors in North America and Europe [32-34], for Hanover, a NAB carrier rate of 9% was demonstrated [33]. As there is no clear association between GBV-C and a specific clinical disease, the virus is tolerated in the human blood supply [31, 34]. For this reason, GBV-C provides a realistic platform for model calculations to the relative infectious risk of specific blood components. Our calculation model included the following data and assumptions: Prevalence of GBV-C RNA-positive donors 1.2%, prevalence of GBV-C NAB-positive donors 0%, 10%, 20%, and 30%, MHH PC transfusion needs 12,319 TU (analogue to the year 2006). Moreover, we presumed that each GBV-C RNA-positive BC would lead to an infectious P-PC, if coincidentally pooled with 3 NAB-negative BC, and conversely, each GBV-C NAB-positive BC would lead to a non-infectious P-PC, if coincidentally pooled with at least 1 GBV-C RNA-positive BC.

Given the prerequisites of PLT transfusion in Hanover with 1,392 apheresis donors necessary for 12,319 A-PCs or 49,276 whole blood donations that would be necessary for the preparation of 12,319 BC-derived P-PCs (table 1), the formula that calculates the rate of GBV-C infectious A-PCs and P-PCs without inclusion of any neutralizing antibodies is shown in table 2. Given the prerequisites of PLT transfusion in Hanover with 49,276 whole blood donations necessary for the preparation of BC-derived P-PCs and including a rate of e.g. 10% GBV-C NAB-positive donors, a mathematical model had to be applied that calculated the probability of infectious preparations (GBV-C RNA-positive) as a percent value of the entire P-PC production. This was calculated by using the MAPLE software program, a general-purpose mathematical software package (version 8.0.1, Maplesoft, Ontario, Canada). The calculation applied a formula (see below) with binomial coefficients, where *IF* corresponds to GBV-C RNA-positive *In*fectious donors ($49,276 \times 0.012 = 591$ individuals); *N* corresponds to donors without evidence of GBV-C infection (negative for GBV-C RNA and GBV-C NAB ($49,276 - 591 = 48,685$ individuals; $48,685 - 10\% = 43,757$ Neutral individuals)); and *IM* corresponds to *IM*mune donors with antibodies to GBV-C only (e.g. for a 10% rate of GBV-C NAB carriers, $48,685 \times 0.10 = 4,869$ individuals).

$$\frac{\binom{N}{3} \binom{IF}{1} + \binom{N}{2} \binom{IF}{2} + \binom{N}{1} \binom{IF}{3}}{\binom{N + IM + IF}{4}} = IF \text{ P-PCs} \quad (1).$$

Results

We present here an analysis that describes the development of PC transfusions in our clinic compared to other labile blood products from 2003 to 2006 and demographic data of the PC transfusion recipients. We calculated in detail the differences regarding donor exposure as a result of a change in transfusion policy from A-PCs to P-PCs, and, using GBV-C as a model, analyzed possible infection rates that could go along with this change.

Table 3. MHH transfusion recipients 2003–2006

Year	Inpatients, n	Transf Rec	PC-Tx-Rec ^a	Total PC-Tx
2003	28,044	4,907	1,308	9,060
2004	31,876	5,714	1,582	9,514
2005	33,605	6,146	1,725	10,591
2006	34,537	6,257	1,774	12,319
Increment				
2003–2006, %	+23.2	+27.5	+35.6	+36.0

Transf Rec = Transfusion recipients (all labile blood components: RCC, FFP, PC); PC-Tx-Rec = platelet concentrate transfusion recipients; Total PC-Tx = total platelet concentrate transfusions.

^aThe numbers do not include a small number of patients (2003, n = 26; 2004, n = 18; 2005, n = 58; 2006, n = 52) with unclear transfusion records; e.g. PC definitely delivered to the operating theatre, but no clear information about transfusion.

Table 4. MHH-PC transfusion recipients 2003–2006, demographics

Year	Total PC-Tx-Rec	Females, %	Age, years (StDev)	Males, %	Age, years (StDev)
2003	1,308	38.03	51 (± 25)	61.97	53 (± 23)
2004	1,582	37.09	53 (± 25)	62.91	54 (± 24)
2005	1,725	36.64	50 (± 25)	63.36	53 (± 24)
2006	1,774	34.05	52 (± 26)	65.95	52 (± 24)

PC-Tx-Rec = Platelet concentrate transfusion recipients; StDev = standard deviation.

Increasing Importance of PC Transfusions

As shown in table 3, the 4-year period from 2003 to 2006 is characterized by a marked rise in PC usage. While the number of MHH patients as well as the number of transfusion recipients in general increased by about 25%, the number of PC transfusion recipients jumped from 1,308 to 1,774 patients (+35.6%). Consistent to this finding, we observed an increase of PC transfusions by 36.0%. Males received PC transfusions more often than females with a slight, but constant rise from 62 to 66% throughout the observation period (table 4).

Donor Exposure for the Whole MHH PC Recipient Group

From 2003 to 2006, the MHH apheresis donor pool comprised around 1,400 individuals who were subjected to roughly 4 platelet aphereses per year (table 1). These donor and procedure numbers were sufficient enough to prepare all A-PCs needed for treatment of MHH patients. As the number of patients with PC transfusion requirements was constantly increasing while the number of A-PC donors remained stable, the donor/patient proportion gradually declined from values slightly above 1 to 0.79 donors per patient per year. If P-PCs would completely replace A-PCs, a total of 36,240 (2003) to 49,276 whole blood donations (2006) would have been at least needed to meet the MHH PC transfusion demands. As it is very unlike-

Table 5. Median donor exposure in platelet concentrate transfusion recipients (PC-Tx-Rec) with low or high PC demands, calculations for 2006

PC-Tx	Recipients, n ^a	Additional blood components		Donor exposure A-PC	Calculated donor exposure P-PC	P-PC donor /A-PC donor ratio ▲
		RCC	FFP			
2 (1–3)	960	6 (0–87)	6 (0–65)	14	20	1.42
8 (7–9)	107	16 (1–82)	12 (0–88)	36	60	1.67
14 (11–20)	138	20 (3–129)	16 (0–91)	50	92	1.84
35 (21–183)	131	35 (4–254)	26 (0–250)	96	201	2.09

^aAll together 1,336 individual patients (75.3%).

ly that a PC recipient would encounter the same donors in subsequent PC pools, the 36,240–49,276 whole blood donations here approximate 36,240–49,276 individual whole blood donors. Therefore, these numbers correspond to a pool donor to patient ratio ranging from 24.1 (2003) to 27.8 (2006) and to a 25- to 35-fold higher donor exposure if the calculated number of whole blood donors necessary for P-PC production is compared with the actual size of the MHH apheresis donor pool (table 1).

Donor Exposure for Individual MHH PC Recipients with Low or High PC Transfusion Demands

Based on data from 2006, we analyzed the influence of applying P-PCs instead of A-PCs on the median donor exposure in groups of individual MHH patients with low or high PC transfusion needs and included their additional demands for other labile blood products (red cell concentrates (RCC), fresh frozen plasma (FFP); table 5). We formed 4 groups of PC recipients with low (1–3 A-PCs), moderate (7–9 A-PCs), high (11–20 A-PCs), and very high numbers of PC transfusions (21–183 A-PCs). The A-PC range steps of 7–9 PC transfusions for ‘moderate’, of 11–20 PC transfusions for ‘high’, and >20 PC transfusions for very high transfusion needs were chosen because they yielded comparable patient group sizes with 107, 138, and 131 individual patients. These 4 groups comprised a total of 1,336 out of 1,774 PC transfusions recipients (75.3%, table 5). To calculate the median donor exposure for the A-PC transfusion groups, the medians for A-PCs, RCC, and FFP were added. To calculate the median donor exposure for the hypothetical P-PC transfusion groups, the medians for platelet transfusions were multiplied by 4, and then the medians for RCC and FFP were added. Our calculations show that P-PC transfusion recipients with PC transfusion needs as low as 1–3 TU will receive a 40% higher donor exposure than the corresponding A-PC transfusion group. Generally, in P-PC recipients the median P-PC/A-PC donor exposure ratio increases with rising numbers of PC transfusions resulting in a duplication of donor numbers in patients with very high PC transfusion needs (+ 109%; table 5).

Donor Exposure for Individual MHH PC Recipients with Hematological Malignancies Compared to Other Diseases

Based on data from 2006, we also analyzed the influence of applying P-PCs instead of A-PCs on the median donor expo-

sure ratio in groups of individual MHH patients with hematological and non-hematological, predominantly surgical diagnoses (solid organ transplantation, cardiac surgical, and poly-trauma patients). This evaluation comprised 1,693 of 1,774 patients (95.4%) with 11,701 PC transfusions (95.0%). The first very interesting finding was that the number of non-hematological PC recipients clearly exceeded the hematological PC patients (952 vs. 741 patients), albeit the latter group comprehended much more PC transfusions (7,525 vs. 4,176 PC transfusions, table 6). Here, we formed 2 groups with ≤ 10 and ≥ 10 PC transfusions. Again, the medians for A-PCs, RCC, and FFP were added for the A-PC patient group. For the hypothetical P-PC transfusion group, the medians for platelet transfusions were multiplied by 4, and then the medians for RCC and FFP were added. As shown in table 6, in hematological patients with ≥ 10 PC needs, PCs are now the leading blood components that are even more often applied than RCC. In both the hematological and the surgical patients, the donor exposure rises with increasing numbers of PC transfusions. The increase in the P-PC/A-PC donor exposure ratio is much stronger in hematological patients than in surgical patients (e.g. 2.25 in hematological patients vs. 1.51 in surgical patients with ≥ 10 PC transfusions. This is due to the higher number of RCC (46 vs. 21) and FFP (32 vs. 11) transfusions in surgical than in hematological patients that diminish the influence of P-PC transfusions on the donor exposure.

Prediction of Infectious Therapeutic Units for Recipients of A-PC vs. P-PC Using GBV-C Viremia among Healthy Blood Donors as a Model

As shown in table 2, marked differences occur if the prerequisites for PC transfusion in Hanover are used to calculate the number of infectious A-PCs compared to P-PCs. For P-PCs, a worst case scenario (no donor has agent-specific NAB), a realistic scenario (10% of the donors have NAB), and scenarios with higher numbers of donors with such antibodies are given. For P-PCs, in the worst case scenario 591 GBV-C RNA-positive donors contaminate their pools and produce infectious therapeutic units. This figure is approximately 4 times higher than the number of GBV-C-contaminated A-PCs (table 2). In the GBV-C analogue realistic scenario with a 10% rate of NAB-positive donors, some GBV-C contaminants are neutralized by the pooling process so that the number of infectious

Table 6. Donor exposure in patients with hematological diseases compared to patients with surgery

	Hematological malignancies ^a		Surgery ^b	
	PC ≤ 10	PC ≥ 10	PC ≤ 10	PC ≥ 10
Patients, n	559	182	818	134
PC	3 (1–10)	23 (11–183)	2 (1–10)	16 (11–82)
FFP	2 (0–75)	11 (0–173)	6 (0–88)	32 (0–250)
RCC	6 (0–129)	21 (1–171)	8 (0–87)	46 (8–254)
Donor exposure A-PC	11	55	16	94
Calculated donor exposure P-PC	20	124	22	142
P-PC donor /A-PC donor ratio ▲	1.82	2.25	1.38	1.51

^a741 patients, 7,525 PC transfusions.

^bSolid organ transplant, cardiac surgery, polytrauma; 952 patients, 4,176 PC transfusions.

TU is reduced from 591 to 423 P-PCs. This figure is still far more than 2 times higher than the number of GBV-C-contaminated A-PCs. A number of at least 30% of NAB carriers is needed to obtain roughly equal rates of infectious products for both A-PCs and P-PCs. In this context, it is noteworthy that our numbers for infectious A-PCs also represent a worst case scenario. This is due to our relatively large donor pool and to our triple platelet apheresis program that is associated with a comparatively high number of split products (MHH 2.23 split products instead of 1.8 split products in other German institutions with a routine double platelet apheresis program).

Discussion

In some European countries and Canada, P-PCs prepared by the BC technique are gradually becoming standard products while the use of A-PCs is more restricted to specific clinical conditions such as PLT refractoriness, supply for newborns with neonatal alloimmune thrombocytopenia (NAIT), and others [16, 35]. In Germany, A-PCs are still preferred, but the proportion of transfused P-PCs has been gradually increasing from 32.3% in 2001 to 37.0% in 2006 [36]. The recent German discussion to select the PC product based on ‘availability only’ [17, 18] has prompted a retrospective study on the usage of PCs at our clinic. Aim of the study was to calculate the increase in donor exposure associated with a universal use of P-PCs instead of A-PCs under current clinical conditions and to determine possible infection rates that could go along with this change. The results of our study carry substantial information to medical professionals who apply PCs.

First, in relation to other labile blood components, PC are becoming more and more important, as in the 4-year period of 2003 to 2006 in Hanover, the number of PC transfusion recipients has increased more than the number of transfusion recipients in general (table 3). Second, if A-PCs are completely replaced by P-PCs, the 2003 through 2006 subgroup of 1,300 to around 1,800 MHH patients with PC transfusion requirements would carry a more than 1 log step higher donor burden as for

example recipients of blood products who are transfused with RCC only. This result was found by calculating the least number of 4 donors per P-PC. This is true for the P-PC donor / MHH PC-recipient ratio as well as for the P-PC donor / MHH A-PC donor ratio (table 1). If higher numbers of donors have to be pooled (e.g. 5 donors per pool), the relationship would be even more unfavorable. We have neglected the influence of repeat whole blood donations from the same donors that theoretically diminish the blood donor burden, as it is very unlikely that a PC recipient encounters the same donors in subsequent PC pools. Thus, 36,240–49,276 whole blood donations here approximate 36,240–49,276 individual whole blood donors. This is an alarming finding because it characterizes P-PC recipients as a risk group in transfusion medicine. It must be assumed that an emerging pathogen in the human blood supply that is unrecognized for a certain period of time will rather accumulate in P-PC recipients than in recipients of SD A-PCs or in recipients of blood components other than PCs. Third, we have calculated the increase in donor exposure in 4 groups of PC recipients with low to very high PC transfusion needs on the one hand, and as a comparison between hematological patients and patients with surgery (cardiac surgery, solid organ Tx, and polytrauma) on the other hand. As shown in tables 5 and 6, the individual patients with P-PC transfusions would experience a 40–125% increase in donor exposure compared to SD PCs regardless of whether low or high PC transfusion needs per patient or the underlying diseases of the patients are considered. In the only comparable study, Lopez Plaza et al. [15] described a higher donor exposure than calculated in this study of up to 400% associated with the exclusive use of P-PCs instead of A-PCs [15]. However, their study from the 1990s was based on 7 donors per P-PC, a realistic assumption for P-PCs prepared by the PRP method in routine use at that time. The BC pooling technique that is nowadays becoming more and more common (especially in Europe), requires a maximum of 4–6 whole blood donations. Unfortunately, a donor restriction to e.g. 3 BCs for a P-PC product is often associated with intolerably low yields of PLT per P-PC (often below the German lower limit of 2×10^{11} PLT/TU) so that a

further reduction of donor exposure appears unlikely. In this context, the relatively high calculated donor exposure in hematological patients (plus 80–125%) going along with P-PC usage is another important finding as this could elevate the rate of patients with PLT refractoriness. Elevated levels of PLT refractoriness for P-PC compared to A-PC usage have been reported by Slichter et al. [12] and the French Hemovigilance Agency [37]. Fourth, one of the most often cited arguments for a change in the transfusion policy from A-PCs to P-PCs is the nowadays low frequency of classical TTI such as HIV or HCV in the donor population [1, 2, 7, 13–22, 35, 38]. In this discussion emerging pathogens in the human blood supply either play a remarkably low role or are discussed in the context of pathogen inactivation. We present here a realistic model for the possible spread of an infection among patients with PC needs in Hanover, if a transfusion transmissible pathogen is not recognized for some time (table 2). The model picks up a known virus, the GBV-C/HGV flavivirus. This virus is endemic in apparently healthy human blood donors at a range of 1–4.5% as shown by NAT testing in the US, France, Germany, and other countries [27–34, 39]. It is not the purpose of this paper to reopen the discussion on the pathogenicity of HGV-C/HGV. We and many others have shown that GBV-C is unlikely to be involved in disease processes [28, 30, 34, 39] and is thus tolerated in the human blood supply. We are also aware that GBV-C/HGV can be inactivated by pathogen reduction systems [2, 4]. We have chosen this virus solely because its frequency and the frequency of its neutralizing antibody are well investigated in healthy humans. For this reason, it can serve as a simulation model to investigate the spread of an unrecognized viral infection with a relatively low frequency around 1% and assuming a frequency of donors with NAB ranging from 0–30% in the general population. As shown in table 2, using the Hanover PC transfusion data, P-PCs will infect nearly 4 times more patients than A-PCs, if no carriers with NAB are present. If a figure of 10% for donors with NAB is assumed (most realistic for GBV-C in developed countries), the contamination rate for P-PCs still is far more than double as high as with A-PCs (424 for P-PCs vs. 152 for A-PCs). The P-PC vs. A-PC contamination rates converge only if donors with NAB exceed a threshold of 30% of the

general population. Thus, this model shows the possible consequences of an uncritical switch of the PC transfusion policy from A-PCs to P-PCs. It also disputes, at least to some degree, the usefulness of agent-specific NAB in the general population. Our calculations clearly show that a high frequency of individuals (more than 30%) with antibodies with sufficient neutralization capacity and sufficient antibody titer are needed to outweigh the disadvantage of a large donor pool.

For obvious reasons, our model has some limitations. For instance, it cannot include factors such as insufficient infection due to defective virus, low virus titer, high dilution by the pooling process, or insufficient neutralization due to missing neutralization capacity, low antibody titer, or dilution of antibodies to an insufficient neutralization level by the pooling process. One might argue that the introduction of pathogen inactivation might eliminate the disadvantage of P-PCs that is correlated with the drastic increase of more than 1 log step in donor exposure compared to A-PCs. However, we must bear in mind that pathogen inactivation procedures are always validated against the past, in particular against transfusion transmissible agents that are already known. To conclude, compared to SD blood components, P-PCs remain dubious blood products. The advantage of maximizing the whole blood donors' gift is outweighed by a more than 1 log step increase in donor exposure to the community of PLT transfusion recipients and to individual patients by 40–120%. A model calculation using the PC transfusion conditions in Hanover and known frequencies of GBV-C RNA and NAB against GBV-C shows that infectious agents with a frequency as low as 1% in the general population can be associated with a 4 times higher contamination rate in P-PC transfusion recipients than in A-PC recipients. Our data suggest that a general change in the transfusion policy from A-PCs to P-PCs is dangerous and must be avoided.

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