

**The Incidence of CNS Bleeding In Transfusion Dependent Patients Before and After Introduction of Pathogen Inactivated Platelet Components Stored For More Than 5 Days:
A Nine Year Hemovigilance Survey**

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Background

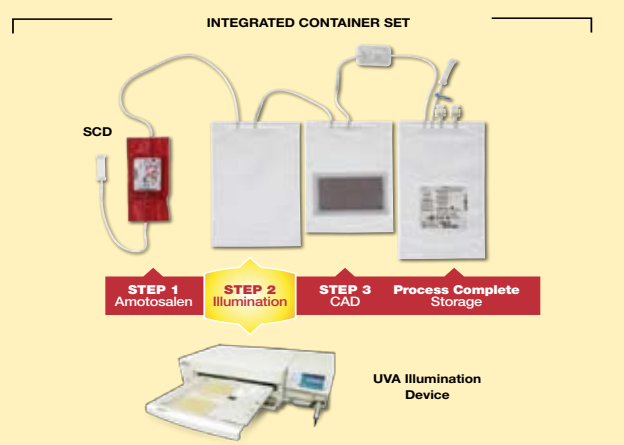
Pathogen inactivation (PI) of platelet components (PC) (INTERCEPT™, Cerus BV, Amersfoort, Netherlands, **Figure 1**) is used in a number of transfusion centres throughout Europe to reduce the risk of transfusion-transmitted infections, including transfusion-related sepsis. In October 2003, use of PI-PC with 5 day storage was routinely implemented by the Blood Transfusion Centre of Mont-Godinne in place of bacterial detection. Because PI demonstrates robust bacteria inactivation, in December 2006 the storage time for PI-PC was

extended to 7 days. Central Nervous System (CNS) bleeding is an infrequent, but serious complication of transfusion-dependent thrombocytopenia, which could be increased if the hemostatic function of treated PC were sub-optimal. Prior studies of hemostatic function using model systems have shown 7 day-old PI-PC retain hemostatic function (*Transfusion* 2007; 47:666). A large (n = 645) randomized controlled clinical trial (*Blood* 2004;104:1534) demonstrated no increase in CNS bleeding with PI-PC stored for 5 days. However,

there is limited information regarding the incidence of CNS bleeding among platelet transfusion-dependent hematology patients supported with PI-PC for long periods and with use of PC stored for more than 5 days. We conducted a retrospective review to determine the incidence of CNS bleeding among platelet transfusion dependent hematology patients repeatedly transfused with PI-PC stored for up to 7 days.

Figure 1: The INTERCEPT Blood System for Platelets

Using a sterile connecting device (SCD), the platelet container is sterilely connected to the INTERCEPT kit. Amotosalen (1) is added by gravity flow and the platelet mixture is illuminated with UVA light (2). Residual amotosalen and its photoproducts in the platelet mixture are reduced to low levels using a compound adsorption device (CAD) (3) before the platelets are transferred to the storage container.



Aims

- To assess the impact of PI on the incidence of CNS bleeding after extension of PI-PC storage to 7 days.
- To determine the incidence of CNS bleeding in hematology patients in the 3 years before introduction of PI-PC, 3 years with use of PI-PC with 5 day storage, and 3 years with use of PI-PC with 7 day storage.

Methods

Transfusion data for all hematology patients hospitalized and transfused at Mont-Godinne during the years 2000 – 2009 were analyzed between 3 treatment periods (Period 1: 01/10/2000–30/9/2003 with conventional PC; Period 2: 01/11/2003 – 30/11/2006 with 5 day PI-PC; Period 3: 01/12/2006 – 30/11/2009 with 7 day PI-PC. Medical records of hematology patients who received platelet components (PC) were reviewed for radiologic examinations (CT scan or MNR imaging studies). All

imaging studies performed within 48 hours following a platelet transfusion were specifically evaluated for a diagnosis of CNS bleeding. The reports were reviewed by a neuroradiologist, and classified as negative or positive for bleeding. CNS bleeding events were classified by anatomic site (subdural, subarachnoid, or parenchymal) without or with confounding etiologic risk factors for CNS bleeding (trauma, abscess, tumor). The number of days of platelet support during which

patients were at risk for CNS bleeding within each period was determined. Bleeding incidence in the three treatment periods was determined based upon the number of bleeding events per 1,000 person-days at risk for hematology patients undergoing platelet support. The event rates were determined for all CNS bleeding events combined. Poisson regression methods were used to model the CNS event rate data to statistically evaluate trends across the three observation periods.

Results

During Period 3, 22% of PCs were stored for more than 5 days prior to transfusion. The incidence of CNS bleeding per 1,000 days of transfusion-dependent platelet support was compared across all three periods for all patients with CNS bleeding events (**Table 1**), for patients with CNS bleeding events with confounding factors for CNS bleeding (**Table 2**), and for patients with CNS bleeding without confounding factors (**Table 3**). There were no significant trends in the incidence of CNS bleeding events for any patient group across the three periods of platelet support with respective p values of 0.84, 0.57, and 0.86 for each of the patient groups analyzed. These data indicate that transfusion of PI-PC stored for up to 5 days (**Period 2**) or for more than 5 days (**Period 3**) were not associated with an increased risk of CNS bleeding either with or without confounding CNS anatomic factors.

Table 1: All CNS Bleeding Events

	Period 1	Period 2	Period 3
Hematology Patients (N)	272	276	276
All CNS bleeding events (N)	10	11	12
Days of platelet support at risk for CNS bleeding	8,593	9,112	9,459
Incidence of all CNS bleeding per 1,000 person-days at risk - estimate [95% confidence interval]	1.16 [0.56, 2.14]	1.21 [0.60, 2.16]	1.27 [0.66, 2.22]

There was no significant trend in the incidence of CNS bleeding across periods (p = 0.8395).

Table 2: CNS Bleeding Events With Confounding Factors

	Period 1	Period 2	Period 3
Hematology Patients (N)	272	276	276
CNS bleeding events with confounding factors (N)	3	4	5
Days of platelet support at risk for CNS bleeding	8,593	9,112	9,459
Incidence of CNS bleeding with confounding factors per 1,000 person-days at risk - estimate [95% confidence interval]	0.35 [0.07, 1.02]	0.44 [0.12, 1.12]	0.53 [0.17, 1.23]

There was no significant trend in the incidence of CNS bleeding with confounding factors across periods (p = 0.5679).

Table 3: CNS Bleeding Events Without Confounding Factors

	Period 1	Period 2	Period 3
Hematology Patients (N)	272	276	276
CNS bleeding events without confounding factors (N)	7	7	7
Days of platelet support at risk for CNS bleeding	8,593	9,112	9,459
Incidence of CNS bleeding without confounding factors per 1,000 person-days at risk - estimate [95% confidence interval]	0.81 [0.33, 1.68]	0.77 [0.31, 1.58]	0.74 [0.30, 1.52]

There was no significant trend in the incidence of CNS bleeding without confounding factors across periods (p = 0.8577).

Review of a nine year experience of hematology patients during platelet transfusion support with conventional and PI-PC stored for up to 5 days or for more than 5 days provided unique data on the risk of CNS bleeding events.

Conclusions

- The introduction of PI-PC did not result in an increased incidence of CNS bleeding with either 5 day or 7 day platelet component storage.
- Retrospective review of large databases to determine the incidence of low frequency outcomes is a useful method to characterize the therapeutic efficacy of platelet transfusion.