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Unintentional Platelet Removal by Plasmapheresis

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Therapeutic plasmapheresis may remove platelets as well as plasma. Unintentional platelet loss, if not recognized, may lead to inappropriate patient assessment and treatment. A patient with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is reported in whom persistent thrombocytopenia was interpreted as continuing active disease; thrombocytopenia resolved only after plasma exchange treatments were stopped. This observation prompted a systematic study of platelet loss with plasmapheresis. Data are reported on platelet loss during 432 apheresis procedures in 71 patients with six disease categories using three different instruments. Comparing the first procedure recorded for each patient, there was a significant difference among instrument types ($P<0.001$); platelet loss was greater with the Fresenius AS 104 (17.5%, N = 21) than with the COBE Spectra (1.6%, N = 26) or the Haemonetics LN9000 (2.6%, N = 24). With all procedures, platelet loss ranged from 0 to 71%. Among disease categories, platelet loss was greater in patients with dysproteinemias who were treated for hyperviscosity symptoms. Absolute platelet loss with the first recorded apheresis procedure, in the 34 patients who had a normal platelet count before the procedure, was also greater with the AS 104 (2.23×10^{11} platelets) than with the Spectra (0.29×10^{11} platelets) or the LN9000 (0.37×10^{11} platelets). In 39 patients in whom data were collected on consecutive days, platelet removal by plasmapheresis correlated with a decreased patient platelet count ($r = 0.40$, $P = 0.011$). In these 39 patients, the platelet counts were significantly decreased at 24 hours ($P = 0.002$).J. Clin. Apheresis. 16:55–60, 2001.

Key words: thrombotic thrombocytopenic purpura (TTP); hemolytic uremic syndrome (HUS); Haemonetics; COBE; Fresenius

INTRODUCTION

The term plasmapheresis implies that only plasma, not blood cells, is removed during the procedure. Many physicians are unaware that platelet loss is a risk with therapeutic plasmapheresis. Although previous reports have documented substantial platelet loss [1–5], this complication is not mentioned in standard texts, procedure manuals, and current reviews [6–8].

We became aware of the potential for platelet loss during the plasma exchange treatment of a patient with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS). Although her acute signs and symptoms resolved, moderate thrombocytopenia persisted in spite of daily plasma exchange. When her platelet count promptly recovered to normal after plasma exchange was stopped, we postulated that unintentional platelet removal during the daily plasma exchanges may have contributed to her persistent thrombocytopenia. To document and quantify this problem, we analyzed platelet loss in 71 patients (432 apheresis procedures) who had therapeutic plasmapheresis for any indication.

CASE REPORT

Mrs. S.W., 50 years old, suddenly noted loss of recent memory and expressive aphasia. When she saw her physician, her symptoms were resolving and were attributed to hypertension. Laboratory data included a platelet count of 23,000/μL, hematocrit 37%, creatinine 0.8 mg/dL, and LDH 547 U/L (normal <233 U/L); the abnormal platelet count and LDH were attributed to artifact because of the difficulty drawing blood. Repeat laboratory data 3 days later demonstrated a platelet count of 20,000/μL, hematocrit 31%, creatinine 1.0 mg/dL, and LDH 572 U/L. She was afebrile. The peripheral blood smear demonstrated red cell fragmentation; urinalysis demonstrated hematuria. A diagnosis of TTP-HUS was made, though the neurologic abnormalities had resolved, and daily plasma exchange with one plasma volume of fresh-frozen plasma was begun [9] with a Fresenius AS 104 instrument by using the pre-programmed plasma: platelet buffy coat interface detector setting (Fig. 1). Her platelet count and LDH became normal (151,000/μL, 184 U/L)

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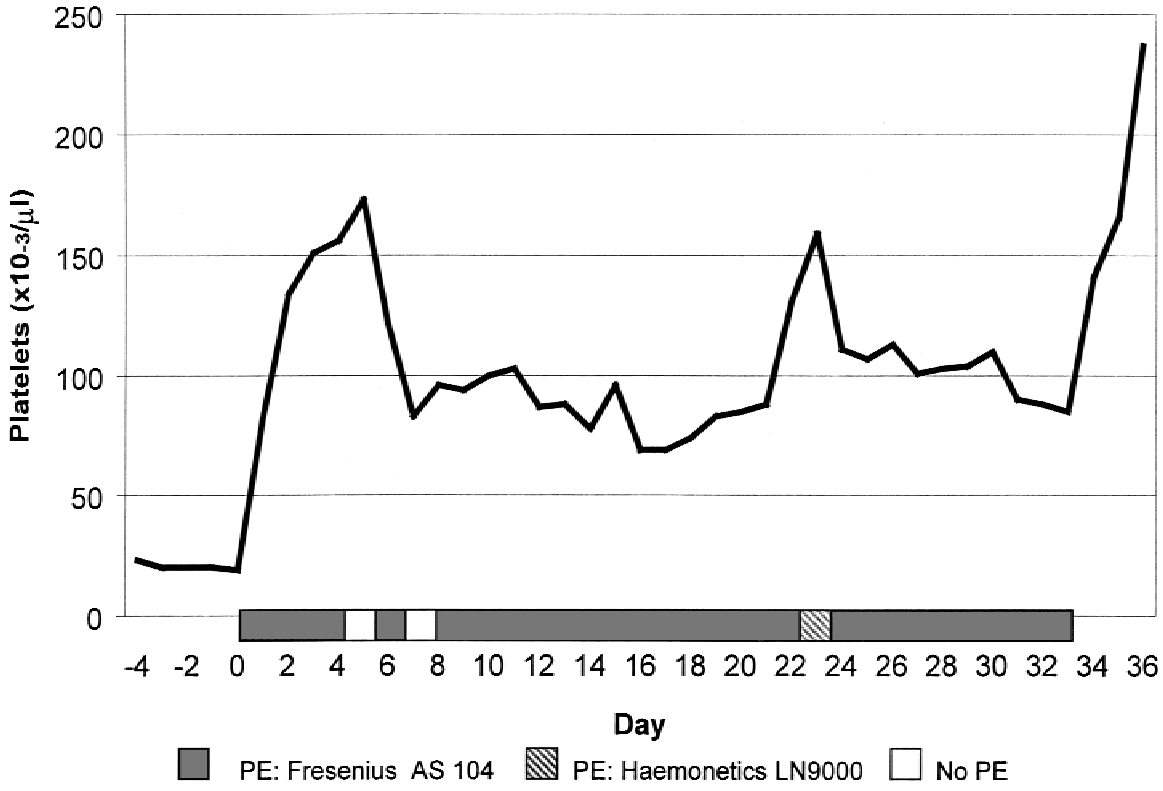

Fig. 1. Clinical course of a patient with TTP-HUS. Daily plasma exchange was begun on day 0. Plasma exchange (PE) frequency was decreased to every-other-day after the platelet count and LDH became normal, however thrombocytopenia recurred and daily plasma exchange was resumed. Thrombocytopenia then persisted until daily plasma exchange was stopped after 35 treatments because of a plasma transfusion reaction. Plasma exchange procedures were performed with a Fresenius AS 104 except for one day when a Haemonetics LN9000 was used. In retrospect, a higher platelet count following use of the Haemonetics LN9000 was appreciated.

after 4 days of plasma exchange; therefore the frequency of plasma exchange was decreased to every-other-day. However thrombocytopenia (83,000/μL) recurred and LDH increased (223 U/L), so daily plasma exchange was resumed. During the next 4 weeks, thrombocytopenia persisted, apparently refractory to plasma exchange; prednisone, 200 mg/day, was begun on the 24th day. Plasma exchange was stopped after 31 treatments because of a plasma transfusion reaction manifested by hypotension, and then her platelet count promptly returned to normal. There was no evidence for active TTP-HUS during the last 3 weeks of treatment except for persistent thrombocytopenia. Mrs. S.W. has been well since.

No platelet counts were performed on the patient's removed plasma; therefore there was no direct evidence that unintentional platelet removal was the cause of persistent thrombocytopenia. However this and similar experiences in other patients were the motivation for this study.

METHODS

Data were obtained on plasmapheresis procedures performed by the Oklahoma Blood Institute (OBI) for 32 weeks: September 27, 1999 to May 9, 2000. The OBI performs all plasmapheresis procedures in the central Oklahoma region, and this study includes data on 71 of 74 (96%) patients and 431 of 686 (63%) procedures during this period. Much of the missing data was due to the lack of laboratory availability to collect data from procedures performed on weekends.

Three instruments were used for plasmapheresis: COBE Spectra (Gambro [COBE BCT], Lakewood, CO), Haemonetics LN9000 (Haemonetics Corp., Braintree, MA), and Fresenius AS 104 (Fresenius AG, Bad Hamburg, Germany). The AS 104 instrument was used with either one of two programs for determining the plasma-platelet interface: 1) a pre-programmed interface detector, which is the manufacturer's default setting, or 2) a hematocrit control program in which an alternate program based on the patient's height, weight, and hematocrit is entered. The latter program, comparable to the data entered for the Spectra instrument, was used in an attempt to more carefully avoid the plasma: platelet interface. Inlet flow rates from the patients were 60–75 ml/min for all instruments in all patients. This was consistent with OBI policy to never exceed 80 ml/min in order to avoid symptoms of alkalosis from citrate toxicity.

TABLE I. Percent Platelet Loss Related to the Apheresis Instrument

Instrument	N	First apheresis[a] [median (minimum, maximum)] percent	N	All apheresis [median (minimum, maximum)] percent
LN9000	24	2.6 (0.4, 26.3)	135	2.6 (0, 26.3)
Spectra	26	1.6 (0, 33.3)	185	1.2 (0, 33.3)
AS 104				
both programs[b]	21	17.5 (3.9, 30.8)	112	18.6 (3.6, 70.7)
program A[b]		—	34	18.9 (3.9, 57.4)
program B[b]		—	77	18.6 (3.6, 70.7)

[a]These data are for the first recorded apheresis procedure for each of the 71 patients. Median rather than mean values are reported since the data were not normally distributed. Using the first recorded apheresis procedure, there was a significant difference of percent platelet loss among the three instruments ($\chi^2 = 30.13$, 2 df, $P < .001$).

[b]Two different AS 104 instrument programs were used: A, pre-programmed plasma-platelet interface program; B, hematocrit control program.

For each procedure, the nurse completed a data collection form including patient's diagnosis, instrument used, control settings, and estimated patient blood volume. Blood volume was calculated as a function of body weight, height, and body type (fat, thin, normal, or muscular) [10]. Each patient's pre-apheresis total body platelet number was determined by the platelet count determined immediately prior to the procedure, multiplied by the estimated blood volume; this product was multiplied by 1.5 to account for the approximately one third of total body platelets sequestered in the spleen [11]. None of the patients in this study had had a splenectomy. The absolute number of platelets removed was determined from the platelet count on an aliquot of the removed plasma multiplied by the volume of the removed plasma, which was determined by weighing the collection bag then converting grams to milliliters.

Platelet loss was expressed either as a percent of total body platelets or as the absolute number of platelets removed. Percent platelet loss allowed for comparisons among all patients, including those who were thrombocytopenic, but could have been inaccurate in some patients if the estimate of the total body platelet number was inaccurate. The absolute number of platelets removed may be dependent on the patient's pre-apheresis platelet count; therefore these calculations were restricted to patients who initially had a normal platelet count.

Patients were assigned to one of six disease categories to determine the influence of disease type: 1) TTP-HUS, 2) neurologic disorders, 3) liver failure, 4) autoimmune disorders, 5) dysproteinemias, and 6) other disorders, which included organ transplant rejection and heparin-induced thrombocytopenia. Neurologic disorders included Guillian-Barre syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, and Eaton-Lambert syndrome; autoimmune disorders included systemic lupus erythematosis and Goodpasture's syndrome; dysproteinemias included Waldenstrom's macroglobulinemia, multiple myeloma, and cryoglobulinemia.

The first treatments for each patient for which data were collected were used for statistical comparisons because these represented comparable independent data, without the bias from the different numbers of treatments for each patient. Data were analyzed in two ways: comparison of different instruments and comparison of different diseases. Both the percent platelets removed and the absolute number of platelets removed were analyzed. To compare mean values across groups (instruments and disease categories), the nonparametric Kruskal-Wallis test (using the chi-square approximation) was used. The paired t-test was used to compare the difference between platelet counts on two consecutive days in the same patient.

RESULTS

Percent platelet loss with different instruments is shown in Table I. The AS 104 was associated with a higher average percent platelet loss than either the Spectra or LN9000 (Table I). Results with both settings of the AS 104 instrument were the same. Substantial platelet losses occasionally occurred with all instruments; maximum losses for each instrument exceeded 25%.

Among disease categories (Table II), percent platelet loss was greater in patients with dysproteinemias, who had plasmapheresis for hyperviscosity symptoms. That the initial hyperviscosity may have contributed to platelet loss by retarding platelet sedimentation is suggested by the observation that the greatest platelet loss occurred with the initial recorded procedures. Platelet loss decreased from 27.8% for initial recorded procedures to 6.3% for all procedures, when data for the AS 104 were omitted (Table II). In patients with liver disease, estimated platelet losses were equal to those in other diseases, when data for the AS 104 were omitted (Table II). The AS 104 instrument was used preferentially in patients with liver failure, who commonly had problems with hypotension, because the lower extracorporeal volume of plasma diminished the occurrence of negative fluid balance.

TABLE II. Percent Platelet Loss Related to Patient Disease Category

	N	First apheresis[a] [median, (minimum, maximum)] percent	N	All aphereses [median, (minimum, maximum)] percent
TTP-HUS				
all instruments	15	3.0 (0, 14.7)	196	1.9 (0, 17.4)
LN9000, Spectra only	14	2.4 (0, 11.7)	192	1.9 (0, 17.4)
Neurological Disorders				
all instruments	23	2.7 (0, 21.3)	92	2.5 (0, 29.8)
LN9000, Spectra only	17	2.4 (0, 5.0)	64	1.6 (0, 13.4)
Liver failure				
all instruments	12	17.9 (1.4, 30.8)	66	19.4 (1.4, 70.7)
LN9000, Spectra only	2	2.2 (1.3, 3.0)	4	2.5 (1.4, 5.0)
Autoimmune disorders				
all instruments	11	1.6 (0.6, 25.2)	35	1.9 (0, 25.2)
LN9000, Spectra only	10	1.6 (0.6, 18.7)	32	1.8 (0, 25.2)
Dysproteinemias				
all instruments	6	27.8 (6.3, 33.3)	22	19.7 (0, 57.4)
LN9000, Spectra only	4	27.8 (6.3, 33.3)	15	6.3 (0, 33.3)
Other disorders				
all instruments	4	5.0 (0, 8.2)	21	8.6 (0, 26.3)
LN9000, Spectra only	3	1.7 (0, 5.0)	13	3.9 (0, 23.8)

[a]These data are for the first recorded apheresis procedure for each of the 71 patients. Median rather than mean values are reported since the data were not normally distributed. Using the first recorded apheresis procedure, there was a significant difference of percent platelet loss among the disease categories, both when all instruments were included in the analysis ($\chi^2 = 27.75$, 5 df, $P < 0.001$) and when the procedures with the AS 104 were omitted ($\chi^2 = 11.11$, 5 df, $P = 0.049$).

Substantial platelet loss occurred in every disease category; maximum losses ranged from 17.4% to 70.7% for all procedures. Among patients treated for TTP-HUS, percent platelet loss ranged from 0 to 17.4%, with a median percent loss of 1.9%. However the AS104 instrument was used in only 4 of these 196 procedures (2%), a practice established after experiences similar to that described above in the Case Report.

The absolute numbers of platelets removed from the 34 patients who initially had a normal platelet count were also extremely variable (Table III). The AS 104 instrument removed 6- to 8-fold more platelets than the LN9000 and the Spectra. Platelet counts 24 hours after plasmapheresis were significantly lower (Table IV). The platelet removal in the 39 patients presented in Table IV correlated with the change in decreased platelet count after plasmapheresis 24 hours ($r = 0.40$, $P = 0.011$). Figure 2A presents the same data shown in Table IV, relating platelet losses to the apheresis instrument; Figure 2B presents platelet counts related to the disease category. The two largest platelet losses occurred with the Spectra; both of these patients were treated for dysproteinemia and hyperviscosity.

TABLE III. Absolute Number of Platelets Removed by Therapeutic Plasmapheresis Related to the Apheresis Instrument*

		Platelets removed	
Instrument	N	median	(minimum, maximum)
LN9000	14	0.37×10^{11}	$(0.07, 1.90 \times 10^{11})$
Spectra	13	0.29×10^{11}	$(0.00, 13.12 \times 10^{11})$
AS 104	7	2.23×10^{11}	$(0.58, 3.13 \times 10^{11})$

*Data were analyzed on 34 of 71 patients who had a normal platelet count prior to their first apheresis procedure for which data were collected. The mean pre-procedure platelet count on these 34 patients was 258,000/μl (range, 166,000–489,000/μl). There was no difference among the three groups ($p = 0.58$). Median rather than mean values are reported for platelets removed because the data were not normally distributed. There was a significant difference of platelet loss among the three instruments ($\chi^2 = 11.65$, 2 df, $P = 0.003$). The high maximum platelet loss with the Spectra instrument was in a patient with dysproteinemia and hyperviscosity, as illustrated in Figure 2A, B.

DISCUSSION

Large, unintentional, and often unappreciated platelet losses can occur with plasmapheresis. Although the magnitude of platelet loss can be great, and can occur with all instruments and in all disease categories, most procedures were associated with negligible loss. No patients developed clinically apparent bleeding problems as a result of the platelet loss. However platelet loss exceeded 25% of the total body platelets in 33 of 432 procedures (8%); the greatest loss was 71%. In 270 of 432 procedures (63%), platelet loss was less than 5%. Unappreciated platelet loss may be particularly important in patients with TTP-HUS; plasmapheresis-induced platelet

TABLE IV. Change of Platelet Counts in Patients Following Therapeutic Plasmapheresis Related to the Apheresis Instrument

		Platelet count ($\times 10^{-3}/\mu l$)		
Instrument	N	before first apheresis	24 hours after first apheresis [median (minimum, maximum)]	Difference
All procedures	39	147 (20, 489)	126 (6, 307)	18 (−35, 297)
LN9000	8	233 (100, 76)	186 (67, 290)	42 (−33, 86)
Spectra	17	179 (20, 489)	159 (6, 307)	16 (−35, 297)
AS 104	14	82 (23, 259)	53 (21, 275)	11 (−26, 55)

Data were analyzed on 39 of 71 patients for whom data were collected on consecutive days. Only the first pair of consecutive plasmapheresis procedures on each patient for which data were collected were analyzed. Patients with TTP-HUS, who may be expected to increase their platelet count in response to therapeutic plasma exchange, were omitted from this analysis. Initial platelet counts were lower in patients treated with the AS 104 because this instrument was used preferentially for patients with liver failure. There was a significant difference between the pre-apheresis and 24-hour post-apheresis platelet counts when all procedures were analyzed together ($t = 3.28$, $P = 0.002$). These are the same data presented in Figure 2A.

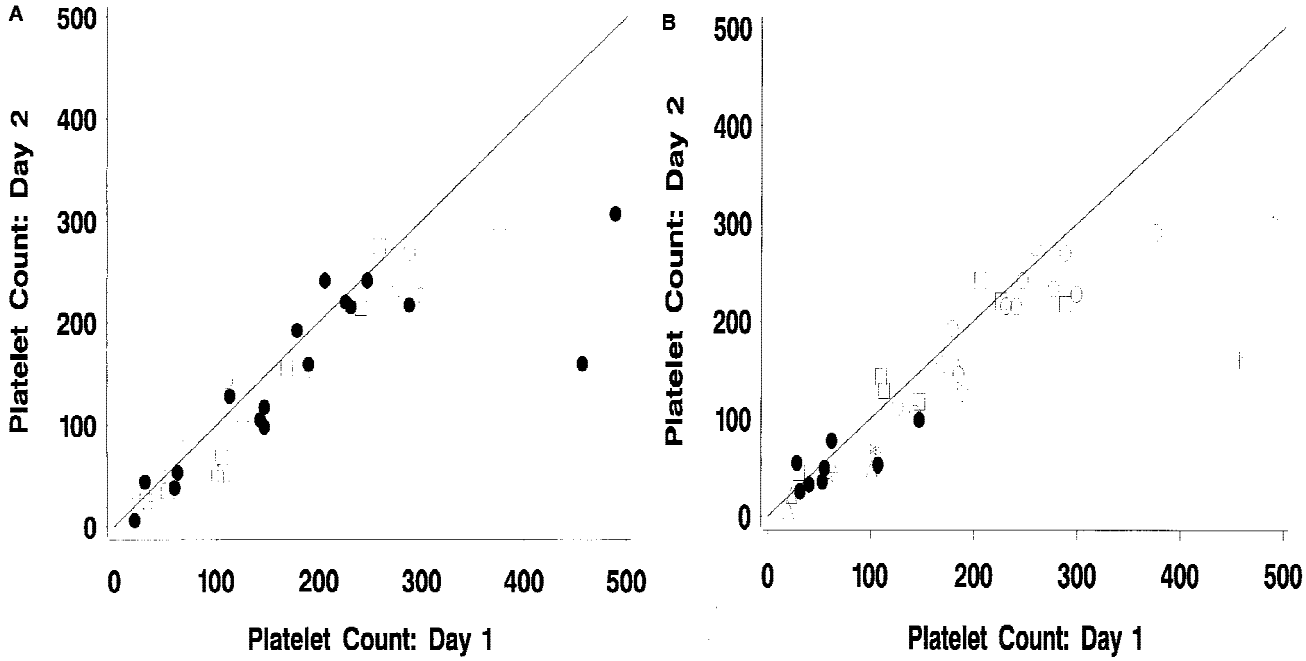

Fig. 2. Data are analyzed on 39 of 71 patients for whom data were collected on consecutive days. Only the first pair of consecutive plasmapheresis procedures on each patient for which data were collected were analyzed. Patients with TTP-HUS, who may be expected to increase their platelet count in response to therapeutic plasma exchange, were omitted from this analysis. Each symbol represents one pair of platelet counts. Symbols below the diagonal line represent a platelet count decrease from day 1 to day 2. There was a significant difference between the pre-apheresis and 24 hour post-apheresis platelet counts when all procedures were analyzed together ($t = 3.28$, $P = 0.002$). **A** and **B** present the same data with different symbols to represent instrument or disease category. A: Platelet counts related to the apheresis instrument: open circle, LN9000; closed circle, Spectra; open square, AS 104. B: Platelet counts related to the patient disease category: open circle, neurologic disorders; closed circle, liver failure; open square, autoimmune disorders; *, dysproteinemias; open triangle, other disorders.

loss may cause persistent thrombocytopenia, which can be incorrectly interpreted as continuing active disease, potentially leading to inappropriate additional treatments.

Substantial platelet losses with plasmapheresis have been previously documented. In four studies using a variety of instruments, platelet counts decreased by 30–53% [1–4]. In these studies there were no bleeding complications and most platelet counts remained within the normal range. However most patients were not treated daily or for prolonged periods. A recent study comparing the AS 104 and Spectra reported essentially the same results documented in this study: in that study mean

platelet loss was 2.1×10^{11} platelets with the AS 104 and 0.1×10^{11} platelets with the Spectra [5]. Some platelet losses in our patients were comparable to the number of platelets removed by intentional plateletpheresis of normal donors (3 to 6×10^{11} platelets) [12].

Platelet losses may be the result of many variables. Higher flow rates may impair plasma-platelet separation by decreasing the time the blood components are exposed to the g-force. Hematocrit settings on the instrument lower than the actual hematocrit may cause removal of platelets; this may occur if red cell transfusions are given concurrently with the plasmapheresis procedure. Hypertriglyceridemia or parenteral nutrition infusions containing lipid emulsions may also obscure the plasma-platelet interface. Increased plasma viscosity may retard platelet sedimentation. These clinical observations suggest that many factors may contribute to unintentional platelet removal, and therefore physicians and apheresis personnel must be alert for platelet loss in all situations.

The apheresis instrument was a significant factor, with greater platelet losses occurring with the Fresenius AS 104 than with the Haemonetics LN9000 or COBE Spectra. Two different instrument settings used with the AS 104, the pre-programmed interface detector and the hematocrit control program, were both associated with the same amount of platelet loss. The greater loss of platelets with the AS 104 may be related to the instrument characteristics, which allow greater efficiency of plasma removal, such as lower g-forces and decreased time of exposure to g-force.

Among disease categories, the greatest platelet loss occurred in patients with dysproteinemias, presumably due to plasma hyperviscosity. Platelet losses in other disease categories were similar. Although mean percent platelet losses in TTP-HUS patients were negligible in this study, this may be related to our policy of not using the AS 104 for these patients.

Physicians and apheresis personnel must be aware that plasmapheresis can cause unintentional platelet loss. This is essential to avoid an incorrect interpretation of thrombocytopenia and inappropriate treatment.

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