Plateletpheresis in the Management of Thrombocytosis

By Edwin G. Taft, Robert B. Babcock, William B. Scharfman, and Anthony P. Tartaglia

Acute thrombotic and hemorrhagic manifestations of thrombocytosis associated with myeloproliferative disorders may be life threatening. Conventional therapy with radioisotopes and/or cytotoxic drugs may require weeks for effective control of platelet counts. In five patients, plateletpheresis by discontinuous-flow (Haemovig) or continuous-flow (Celltrifuge) centrifugation was used as a means of reducing platelet counts acutely. With each procedure, approximately $2-9 \times 10^{13}$ platelets were removed, resulting in decrements in platelet counts and relief of symptoms. Plateletpheresis is a useful and safe acute means of controlling platelet counts in myeloproliferative disorders.

MARKEDLY INCREASED PLATELET COUNTS in polycythemia vera, essential thrombocytosis, other myeloproliferative disorders, or postsplenectomy patients may contribute to life-threatening thrombotic and/or hemorrhagic complications. Several days to weeks are usually required to reduce platelet counts to less hazardous levels, using either $^{32}$P or cytotoxic drugs. We describe five patients in whom plateletpheresis by centrifugation systems has been used effectively to reduce platelet counts until the proliferative rate could be controlled by definitive therapy.

MATERIALS AND METHODS

Plateletpheresis was accomplished in two patients (M.J. and G.D.) with the Haemovig model 10 discontinuous-flow centrifugation device (225 ml bowl), 6-10 passes per procedure, using acid-citrate-dextrose (ACD-A) as anticoagulant. In the first patient (M.J.), manual 2-4-unit plateletphereses were also done between discontinuous-flow centrifugation procedures.

In three other patients (N.P., N.D., and C.O.) direct plateletpheresis with the Aminco Celltrifuge continuous-flow centrifuge was used for acute management. In this procedure, heparin and ACD-A were used as anticoagulants, with protamine infusion into the return line for two patients (N.D. and C.O.). The centrifuge bowl was run at a speed of 1600 rpm, and platelets were removed through the white blood cell ports at a flow rate of 2-10 ml/min.

Platelet counts were determined by standard phase-contrast microscopy methods, and yields of platelets removed were estimated by the general formula:

\[
\text{net weight of platelet concentrate in grams} \
\times \text{no. of platelets/ml} \\
1.027 \text{ g/ml (density of plasma)}
\]

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RESULTS

Patient 1

M.J. was a 43-yr-old woman in whom a diagnosis of polycythemia vera was made in 1966. Multiple phlebotomies and occasional busulfan were primary therapeutic modalities. In late 1973, a splenectomy was done at another hospital, and postoperatively platelet counts rose to 2000-4000 × 10⁹/liter. In January and March 1974, she had two separate cerebrovascular events. The second resulted in a right hemiparesis, following which she was transferred to Albany Medical Center Hospital. Admission blood counts included: platelet count 4200 × 10⁹/liter, white count 91 × 10⁹/liter (77% segmented neutrophils), hemoglobin 7.2 g/dl, and hematocrit 30%. Six separate discontinuous-flow centrifugation plateletphereses, four manual plateletphereses, ³²P, triethylenenelamine, and hydroxyurea over 7 wk were required to maintain the platelet count under 2000 × 10⁹/liter (Fig. 1).

Patient 2

G.D., a 54-yr-old man, was transferred to the Albany Medical Center Hospital in January 1975 following a suspected pulmonary embolism associated with a rapidly rising platelet count 7 days after splenectomy at another hospital. Splenectomy was undertaken for a suspected delayed splenic hematoma following abdominal trauma. Admission blood counts included: white count 14.1 × 10⁹/liter (81% segmented neutrophils), hemoglobin 10.9 g/dl, hematocrit 34.5%, and platelet count 1705 × 10⁹/liter. A recurrent pulmonary embolus on the day of transfer was suspected. Hydroxyurea and ³²P were administered, and two discontinuous-flow centrifugation plateletphereses were undertaken for the control of platelet counts (Fig. 2). Relief from recurrent dyspneic episodes was immediate. No further episodes of suspected pulmonary embolism occurred. Marrow chromosomal analysis revealed the presence of a Philadelphia (Ph¹) chromosome, and marrow morphology was consistent with chronic granulocytic leukemia.

Fig. 1. Hospital course of patient M.J., 43-yr-old female with polycythemia vera (post-splenectomy). Numbered arrows indicate platelet aphereses by discontinuous-flow centrifugation, with asterisks indicating 2-4-unit manual plateletphereses. Rate of platelet count reaccumulation was not appreciably lessened until seventh week of hospitalization.
HYDROXYUREA, gram/day
0, 5

PLATELETS x 10^9/liter

Fig. 2. Hospital and early posthospital course of patient G.D., 54-yr-old male with chronic granulocytic leukemia. Following the two plateletphereses, no further episodes of apparent pulmonary embolization (as on day -2, day 1) occurred.

Patient 3

N.P., a 65-yr-old woman with polycythemia vera diagnosed in 1959 underwent splenectomy for recurrent splenic pain with melphalan preparation in April 1975, with postoperative platelet counts rising to 900 x 10^9/liter. In late November 1975, she experienced pain and swelling in the right lower extremity, a painful right hand with plethoric discoloration, and right-sided headache. At this time her platelet count was 1185 x 10^9/liter. Melphalan was reinstituted at 6 mg/day, and she underwent continuous-flow centrifugation plateletpheresis, with immediate relief of pain in the extremities and headache. Upper extremity pain recurred with increasing platelet count, and was relieved promptly following each of two additional plateletphereses (Fig. 3).

Patient 4

N.D., a 56-yr-old man, underwent cardiac catheterization with subsequent porcine aortic valve heterograft and single saphenous-vein coronary artery bypass graft at another hospital in August 1975, at which time a hemoglobin of 18 g/dl was recorded. In May 1976, he was admitted to the Albany Medical Center Hospital with severe anginal chest pain, electrocardiographic changes consistent with ischemia, and gastrointestinal bleeding from a duodenal ulcer. Admission blood counts included: hemoglobin 15.6 g/dl, hematocrit 52%, white count 42 x 10^9/liter, and platelets 1900 x 10^9/liter. Severe hypertension

Fig. 3. Hospital and early posthospital course of patient N.P., 65-yr-old female with polycythemia vera–myelofibrosis (post-splenectomy). Rate of platelet count increment after each plateletpheresis slowed, demonstrating effect of melphalan on platelet production. Following posthospital 32P, platelet count has been in 400–600 x 10^9/liter range over a 6-mo period.
of 200/110 mm Hg was treated by nitroprusside drip infusion, and he was admitted to the coronary care unit. Direct plateletpheresis by continuous-flow centrifugation was performed twice on the ward, with stabilization of his general condition. He experienced no anginal pain following the first plateletpheresis, and gastrointestinal blood loss ceased within 48 hr. Subsequent therapy included $^{32}$P, hydroxyurea, and a repeat plateletpheresis (Fig. 4).

**Patient 5**

C.O., a 47-yr-old woman, presented with a 3-day history of progressive right facial and right upper extremity sensory deficit, and a right upper extremity paresis. She was found to have the following blood counts: platelets $1135 \times 10^9$ /liter, white count $18 \times 10^9$ /liter, hemoglobin 14.4 g/dl, and hematocrit 42%.

Because of poor venous access, an external arteriovenous shunt was created, and three plateletphereses by continuous-flow centrifugation over a period of 2-wk, in combination with oral melphalan, reduced the platelet count to normal levels (Fig. 5). There was no further progression of neurologic deficit following
the first plateletpheresis, and marked improvement in motor and sensory function was observed during the first week of hospitalization.

DISCUSSION

Previous reports have demonstrated the ability to reduce platelet counts by plateletpheresis in patients with thrombocytosis using manual methods and discontinuous-flow or continuous-flow centrifugation devices. We have confirmed these observations and have found rapid plateletpheresis to be effective in preventing additional morbidity in patients with thrombocytosis by removing large numbers of circulating platelets. We believe that patients with thrombotic or hemorrhagic symptoms associated with thrombocytosis should be treated urgently by plateletpheresis in combination with myelosuppressive therapy.

The numbers of platelets removed per plateletpheresis equalled or exceeded those previously reported. We now attempt to reduce the platelet count to under $500 \times 10^9/liter$ at each procedure, generally requiring the passage equal to two blood volumes over 3–4 hr. In the absence of adequate venous access, a temporary external arteriovenous shunt simplifies the procedure, as in patient 5. No difficulties with clotting of the shunt have been encountered.

Both discontinuous-flow centrifugation (Haemonetics) and continuous-flow centrifugation (Aminco) devices have proved effective in plateletpheresis. The continuous-flow system offers the advantages of a smaller extracorporeal volume in an unstable patient, the ability to avoid citrate toxicity occasionally seen in normal plateletpheresis donors using the discontinuous-flow procedure, and quieter operation on critical-care nursing units. The current lack of a disposable centrifuge bowl for the continuous-flow centrifuge is a potential disadvantage when an Australia antigen (HBsAg)-positive or status unknown patient must be treated. If $^{32}$P has been given, there is a possibility of contamination of the bowl, although the short half-life of $^{32}$P lessens this concern.

Generally, 18–20 days were required for control of platelet counts by medical therapy (except for patient M.J.) and most patients required 2–3 procedures before control was achieved. Additional details of the plateletphereses are given in Table 1.

Despite anecdotal claims by several continuous-flow centrifuge users that high platelet counts cause clumping and obstruction in the rotational-stationary interface, platelet clumping has not been a problem if (1) the white cell pump is kept operating continuously at $>1–2$ ml/min; (2) ACD is added to the afferent tubing at approximately 2 ml/min, and (3) the openings of the white cell ports in the bowl are kept in the central (inner) area of the platelet layer and are not permitted to enter the white or red cell layer.

The relief of symptoms in patients 2, 3, 4, and 5 following plateletpheresis was dramatic. In patient G.D., no further episodes of presumptive pulmonary embolism were observed. In patient N.P., upper extremity discomfort was alleviated following each plateletpheresis, and the unilateral lower extremity edema was relieved after the first plateletpheresis without recurrence. Following the first plateletpheresis, patient N.D. experienced no further anginal pain, gastrointestinal bleeding ceased within 48 hr, and there was striking subjective
improvement in his overall condition. Patient C.O. experienced no further progression in neurologic symptoms and was observed to recover considerable function following the first plateletheresis.

We have found plateletheresis to be a useful measure in reducing the platelet count rapidly and relieving patients of acute symptoms attributed to the elevated platelet counts in thrombocytosis associated with myeloproliferative disorders. We believe that the procedure may reduce the morbidity associated with hemorrhagic or thrombotic manifestations of thrombocytosis during the period between administration and maximum effectiveness of radioisotope or cytotoxic therapy.

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