Erythrocytapheresis Therapy to Reduce Iron Overload in Chronically Transfused Patients With Sickle Cell Disease

By Haewon C. Kim, Noreen P. Dugan, Jeffrey H. Silber, Marie B. Martin, Elias Schwartz, Kwaku Ohene-Frempong, and Alan R. Cohen

Chelation therapy with deferoxamine is effective in preventing the risk of transfusional iron overload, but treatment failure is common because of noncompliance. To reduce the transfusional iron load, we have evaluated long-term erythrocytapheresis in 14 subjects with sickle cell disease and stroke (11) or other complications (3) as an alternative to simple transfusion. Subjects were treated with erythrocytapheresis using the Haemonetics V90 (Haemonetics Corp, Braintree, MA) to maintain the target pretransfusion hemoglobin S (Hb S) level less than 50% for 6 to 71 months. The transfusional iron load and the donor blood usage were analyzed for a 6- to 36-month study period and were compared with similar data from a subset of 7 subjects previously treated with conventional (target Hb S < 30%) and modified (target Hb S < 50%) simple transfusion protocols. The effect of erythrocytapheresis on iron accumulation was determined by assessment of serum ferritin levels in the absence of iron chelation. The mean transfusional iron load and donor blood usage with erythrocytapheresis were 19 ± 14 mg iron/kg/yr (range, 6 to 50) and 188.4 ± 55.2 mL packed-red blood cells (RBC)/kg/yr (range, 107 to 281), respectively. Of 6 subjects receiving no iron chelation therapy, 5 maintained normal or nearly normal serum ferritin levels during 11 to 36 months of erythrocytapheresis. In comparison with conventional simple transfusion and modified simple transfusion, erythrocytapheresis reduced iron loading by 87% (P < .01) and 82% (P < .01), respectively, but increased donor blood usage by 23% and 73%, respectively. Subjects with pre-erythrocytapheresis Hb levels ≥8.0 g/dL had lower iron accumulation (P < .001) and less donor blood usage (P < .005) than subjects with Hb levels <8.0 g/dL. Although donor blood usage is increased in comparison with simple transfusion, long-term erythrocytapheresis markedly reduces or prevents iron accumulation. This form of transfusion therapy allows the cessation of iron chelation in well-chelated subjects and, if used as the initial form of transfusion therapy, may prevent long-term complications of sickle cell disease without risk of iron overload and the need for chelation therapy.

© 1994 by The American Society of Hematology.

Iron overload is a predictable complication of long-term transfusion therapy, and many subjects with sickle cell disease are treated with the iron chelating drug deferoxamine to remove excessive iron and to prevent iron-induced organ damage. However, chelation therapy is associated with serious problems including high cost, difficulty of administration, and numerous side effects. In the management of iron overload, the reduction of the rate of iron loading by modification of transfusion methods is an alternative to the removal of previously stored iron by chelation therapy. We and others have previously shown that the use of a target pretransfusion Hb S level of 50% rather than of 30% reduces transfusion requirements, although the long-term effect of this approach for prevention of recurrent stroke is still under investigation. The reduction in net blood requirements may be enhanced by using manual or automated partial exchange transfusion in place of simple transfusion. We have subsequently expanded our investigation of long-term, automated, partial exchange transfusion or erythrocytapheresis in the prevention of recurrent stroke to determine the range of net blood requirements and of the exposure to donor blood in a larger group of subjects, to identify factors influencing the effect of erythrocytapheresis on net blood requirements, to investigate the feasibility of long-term erythrocytapheresis, and to study the effect of erythrocytapheresis on iron loading and on the need for chelation therapy.

MATERIALS AND METHODS

Subjects. A total of 14 subjects with sickle cell disease who are currently 14 to 29 years old were enrolled in the study. These subjects were chosen for erythrocytapheresis therapy on the basis of high iron loads, poor chelation use, and good venous access. Of these 14 subjects, 11 with homozygous sickle cell disease (Hb SS) had a previous thrombotic stroke; 2 (1 with Hb SS and 1 with Hb S, thalassemia) had debilitating painful crises; and 1 with Hb SS had recurrent priapism. The mean age at the initiation of erythrocytapheresis was 18 years (range, 12 to 24).

Study period. The 14 subjects were treated with erythrocytapheresis to maintain a target pretransfusion Hb S level of 50% for 6 to 71 months. Of these subjects, 7 previously received simple transfusion to maintain a pretransfusion Hb S level of 30% for 47 to 128 months. Of the 7, 1 was treated for 36 months after an Hb S level of 82% was reached.

© 1994 by The American Society of Hematology.

0006-4971/94/8304-001$00/0

From www.bloodjournal.org by guest on October 23, 2017. For personal use only.
months and a pretransfusion Hb S level of 50% for 12 to 36 months. The study period for each subject comprised the 6 to 36 most recent months of each transfusion protocol. The time period required to reach the target Hb S level at the beginning of transfusion therapy or the time period when the target Hb S level was raised from 30% to 50% was excluded from the data analysis.

**Transfusion protocols.** Erythrocytapheresis was performed with the Haemonetics V50 Blood Cell Processor (Haemonetics Corp., Braintree, MA) using a pediatric apheresis set (no. 11010). A one-arm procedure was performed by placing an 18-gauge needle into the antecubital vein. Subjects were not enrolled in the study unless peripheral venous access was adequate. None of the subjects had indwelling catheters for venous access. Flow rates were 20 to 60 mL/min. Normal saline was infused before the first draw if extracorporeal volume exceeded 10% of the subject’s blood volume. Approximately 150 mL of blood with a hematocrit (Hct) level ranging from 47% to 55% was removed per pass. For subjects with pre-erythrocytapheresis Hb levels of 8.0 g/dL or higher, the blood removed during the first one to four passes was replaced with autologous plasma and normal saline rather than with donor blood. This approach enhances the removal of patient rather than donor red blood cells (RBC). For subjects with pre-apheresis Hb levels less than 8.0 g/dL, replacement with donor packed-RBC began after the first draw to avoid severe anemia. The post-apheresis Hb level was 9.0 to 10.0 g/dL. Subjects were maintained at a target preapheresis Hb S level of 50% or below with erythrocytapheresis. An example of the erythrocytapheresis procedure is shown in Table 1.

Seven subjects were treated initially with simple transfusions and received one or two units of donor packed-RBC every 3 or 4 weeks to maintain a target pretransfusion Hb S level of 30% (conventional simple transfusion) and, after 3 or more years without recurrent stroke, an Hb S level of 50% (modified simple transfusion). Although the remaining 7 subjects received some simple transfusions before erythrocytapheresis, details of their simple transfusion therapy were not available.

**Net RBC load and donor packed-RBC usage.** The net RBC load was defined as the gain or loss of RBC volume per kilogram of body weight with each transfusion. RBC volume was calculated using an average spun Hct level of 75% for donor packed-RBC and a measured spun Hct level for blood removed from the subject. Net RBC load reflects the rate of transfusion iron loading.

Donor packed-RBC usage was defined as the total volume of donor packed-RBC per kilogram of body weight administered with each transfusion. Donor packed-RBC usage reflects the rate of exposure to donor blood.

Yearly net RBC load and donor packed-RBC usage were calculated by summation and annualization of the values for each transfusion protocol during the study period.

**Laboratory studies.** Complete blood counts, reticulocyte counts, and Hb S levels were determined before each transfusion; complete blood counts and Hb S levels were also determined after each erythrocytapheresis. Serum ferritin levels were measured every 3 months. Complete blood counts were performed using a Coulter Counter Model S-Plus IV (Hialeah, FL). The Hb S level was expressed as a percentage of total Hb by scanning the cellulose acetate membrane with a densitometer after Hb electrophoresis at pH 8.6. The serum ferritin assay was performed by the microparticle-capture enzyme immunoassay.

**Informed consent.** The Institutional Review Board of the Children’s Hospital of Philadelphia (Philadelphia, PA) approved and approved the study. Informed consent was obtained from subjects and/or parents.

**Statistical analysis.** For comparison of annual net RBC load and packed-RBC usage with erythrocytapheresis (Hb S < 50%) and conventional simple transfusion (Hb S < 30%) or modified simple transfusion (Hb S < 50%), significance levels were determined using the two-sided paired Wilcoxon Signed Ranks test. Hematologic data were compared using the Student’s t-test for grouped samples.

**RESULTS**

**Hematologic data.** Hematologic data for each transfusion protocol are summarized in Table 2. The mean pretransfusion Hb and Hct levels with erythrocytapheresis were similar to those with a conventional or modified simple transfusion protocol. However, mean reticulocyte counts were significantly lower when the Hb S level was maintained below 30% by simple transfusion rather than maintained below 50% by simple transfusion or erythrocytapheresis (P < .05). The pre- and post-erythrocytapheresis Hb and Hct levels did not differ. The mean reduction in Hb S level during the erythrocytapheresis procedures was 42%. Of the 14 subjects, 11 had mean preapheresis Hb levels higher than 8.0 g/dL, and 3 had levels lower than 8.0 g/dL (see Materials and Methods).
Iron overload is well recognized as a life-threatening complication of long-term transfusion therapy. Subjects with sickle cell disease on long-term transfusion programs seem to be as susceptible to iron-induced toxicity, including cardiac abnormalities and death, as are thalassemic subjects.16-17 Clinical trials in subjects with thalassemia major and sickle cell disease have shown the effectiveness of long-term chelation therapy with defer oxamine in inducing negative iron balance, preventing organ dysfunction, and prolonging survival.3,18-20 Despite these positive results, many subjects still experience significant morbidity and early death from iron overload. The major reason for treatment failure with deferoxamine is poor compliance. One-third of

**Table 2. Comparison of Hematologic Data Between Erythrocytapheresis and Two Simple Transfusion Protocols**

<table>
<thead>
<tr>
<th></th>
<th>Pretransfusion</th>
<th>Posttransfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional Simple Transfusion (Hb &lt;30%)</td>
<td>Modified Simple Transfusion (Hb &lt;50%)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hb (g/dL)*</td>
<td>9.7 ± 0.5</td>
<td>9.3 ± 0.6</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>28 ± 2</td>
<td>27 ± 2</td>
</tr>
<tr>
<td>Reticulocyte count (%)*</td>
<td>8.4 ± 1.4</td>
<td>12.4 ± 1.9</td>
</tr>
<tr>
<td>Hb S (%)</td>
<td>20.8 ± 4.0</td>
<td>39.8 ± 5.4</td>
</tr>
</tbody>
</table>

Abbreviations: ND, not done.

* Mean ± 1 SD.

**Transfusion data.** For a single erythrocytapheresis procedure, the mean net RBC load and packed-RBC usage were 1.2 ± 0.9 mL RBC/kg (range, 0.3 to 3.8) and 12.7 ± 3.1 mL packed-RBC/kg (range, 8.2 to 20.8), respectively. The mean duration of the procedure was 119 ± 16 minutes (range, 82 to 145), and the mean interval between the erythrocytapheresis procedures was 3.7 ± 0.6 weeks (range, 2.9 to 5.2).

The mean annual net RBC load and packed-RBC usage were 17.1 ± 12.5 mL RBC/kg/yr (range, 5.4 to 46.1) and 188.4 ± 55.2 mL packed-RBC/kg/yr (range, 107.2 to 280.5), respectively. In the 11 subjects with Hb levels greater than 8.0 g/dL, the mean annual net RBC load and packed-RBC usage were 11.1 ± 2.8 mL RBC/kg/yr and 168.2 ± 42.6 mL packed-RBC/kg/yr, respectively. For the 3 subjects with Hb levels less than 8.0 g/dL, mean annual net RBC load and packed-RBC usage were 39.3 ± 6.7 mL RBC/kg/yr and 262.6 ± 16.1 mL packed-RBC/kg/yr, respectively. The net RBC load (P <.001) and packed-RBC usage (P <.005) differed significantly between subjects with preapheresis Hb levels greater than 8.0 g/dL and less than 8.0 g/dL. All subjects tolerated erythrocytapheresis well. The only side effect was mild hypotension that was easily reversed by infusion of normal saline.

**Effect of long-term erythrocytapheresis on iron accumulation.** To evaluate the effect of long-term erythrocytapheresis on transfusional iron accumulation, net RBC load was converted to net iron load; each milliliter of erythrocytes (RBC) provides approximately 1.08 mg of iron. The annual transfusional iron load for all 14 subjects was 6 to 50 mg iron/kg/yr, with a mean value of 19 ± 14 mg iron/kg/yr (Fig 1). In contrast, in the 7 subjects treated with the conventional and modified simple transfusion protocols, the annual iron loads were 116 to 210 mg iron/kg/yr (mean, 144 ± 32) and 76 to 171 mg iron/kg/yr (mean, 107 ± 41), respectively (Fig 1). The annual iron load was significantly increased in the 3 subjects (subjects no. 1, 2, and 10) with preapheresis Hb levels lower than 8.0 g/dL compared with the iron load in the 11 subjects with Hb levels higher than 8.0 g/dL (P <.001).

After 3 to 6 years of transfusion therapy, 8 subjects were treated with daily subcutaneous infusions of deferoxamine. Of these subjects, 5 later received high-dose deferoxamine by daily intravenous infusion through indwelling catheters because of severe iron overload and poor compliance with subcutaneous therapy. When their serum ferritin levels fell below 350 µg/L after 9 to 12 years of chelation therapy and after 20 to 46 months of erythrocytapheresis therapy, deferoxamine therapy was discontinued in subjects no. 2, 3, 6, and 7 (Fig 2). Subjects no. 9 and 11 had serum ferritin levels of 618 µg/L and 431 µg/L, respectively, when placed on erythrocytapheresis. These subjects never received deferoxamine. In 5 of the 6 subjects in whom deferoxamine was either discontinued or never begun, ferritin levels have remained stable or decreased during 11 to 36 months of erythrocytapheresis therapy (Fig 2). These 5 subjects had preapheresis Hb levels higher than 8.0 g/dL. The ferritin level has increased in 1 subject (subject no. 2) whose preapheresis Hb levels had been lower than 8.0 g/dL; the rate of increase in ferritin level in this subject is still less than one-third of that found with conventional simple transfusion without chelation therapy.

**Comparison of erythrocytapheresis protocol with simple transfusion protocol.** Comparisons of the annual net RBC load and the annual donor packed-RBC usage for the subset of 7 subjects treated with erythrocytapheresis, conventional simple transfusion, and modified simple transfusion are shown in Tables 3 and 4. The mean annual net RBC load with erythrocytapheresis was 87% lower than with conventional simple transfusion (P <.01) and 82% lower than with modified simple transfusion (P <.01). In contrast, the annual packed-RBC usage with erythrocytapheresis was 23% higher than with conventional simple transfusion (P <.02) and 73% higher than with modified simple transfusion (P <.01). No change in clinical indications for transfusion occurred during these studies.

**DISCUSSION**

Iron overload is well recognized as a life-threatening complication of long-term transfusion therapy. Subjects with sickle cell disease on long-term transfusion programs seem to be as susceptible to iron-induced toxicity, including cardiac abnormalities and death, as are thalassemic subjects. Clinical trials in subjects with thalassemia major and sickle cell disease have shown the effectiveness of long-term chelation therapy with deferoxamine in inducing negative iron balance, preventing organ dysfunction, and prolonging survival. Despite these positive results, many subjects still experience significant morbidity and early death from iron overload. The major reason for treatment failure with deferoxamine is poor compliance. One-third of
Fig 1. Annual transfusional iron load in each subject treated with erythrocytapheresis (target Hb S < 50%). The hatched bar and vertically striped bar represent mean annual transfusional iron load in 7 subjects treated with conventional simple transfusion (target Hb S < 30%) and modified simple transfusion (target Hb S < 50%), respectively. Our subjects with sickle cell disease and stroke who have been regularly transfused are poorly compliant with iron chelation.

As an alternative to removing excessive iron by chelation therapy, investigators have tried several approaches to reduce iron accumulation by decreasing blood requirements. These include splenectomy, young RBC transfusion, and modification of transfusion regimens. Erythrocytapheresis is a safe, simple, and efficient method for lowering the Hb S level. This technique, which has been used primarily for the prevention or management of acute, severe complications of sickle cell disease, may also be safe, simple, and efficient for reducing iron accumulation during long-term transfusion therapy. However, there is no published experience on the use of erythrocytapheresis for long-term transfusion therapy in sickle cell disease other than for the prophylactic management of pregnant subjects. Furthermore, there is little information on the effect of long-term erythrocytapheresis therapy on iron accumulation in transfusion-dependent subjects with sickle cell disease.

The present study shows that the annual net RBC load and, therefore, the rate of iron loading were significantly reduced with long-term erythrocytapheresis in comparison with those for simple transfusion. The greatest reduction was found in subjects with preapheresis Hb levels higher than 8.0 g/dL. Under these conditions, the contribution of transfusional iron from each erythrocytapheresis procedure was almost negligible. With the use of an erythrocytapheresis program in which the Hb level is maintained above 8.0 g/dL and the Hb S level is maintained below 50%, we estimate that it will take 6 to 18 years to accumulate as much iron as during 1 year of simple transfusion therapy to maintain the Hb S level below 50%. Such a slow rate of iron accumulation should result in postponement of iron-induced organ damage, thus prolonging life. Even without chelation therapy, some subjects may never have severe complications of iron overload during long-term treatment with erythrocytapheresis. In fact, this approach allowed cessation of iron chelation therapy in 4 subjects in this study and precluded the need for chelation therapy in 2 others. It is of interest that serum ferritin levels continued to decline in 5 of these 6 subjects despite a positive, but minimal, net RBC load. Although it is not clear why the serum ferritin levels decreased, the small amount of additional urinary iron excretion found in patients with sickle cell disease may be sufficient to offset the small amount of transfusional iron loading.

Fig 2. Effect of long-term erythrocytapheresis therapy on serum ferritin levels in the absence of iron chelation therapy with deferroxamine.
gest that the benefits of erythrocytapheresis in preventing transfusion-transmitted infection and alloimmunization may not be increased with erythrocytapheresis therapy compared with that for simple transfusion. Nonetheless, the increased donor exposure associated with erythrocytapheresis may promote early onset of alloimmunization, particularly for patients just beginning transfusion therapy. In our study, no subject developed new antibodies while treated with this technique.

Manual exchange transfusion is more widely available and less expensive than erythrocytapheresis. However, in the usual procedure for manual exchange transfusion, a large aliquot of the subject's blood is removed and immediately replaced by one unit of donor packed-RBC. This method reduces net blood requirements in comparison with simple transfusion, but it is not as effective as the method for erythrocytapheresis used in this study. The procedure for manual exchange transfusion could be altered to more closely resemble our method of erythrocytapheresis, but this alteration would require not only additional time and labor but also, more importantly, special attention to patient safety. The additional cost of $20,000 to $25,000 per year associated with erythrocytapheresis, in comparison with simple or manual exchange transfusion, is partially or fully offset by the reduction or elimination of the cost of iron chelation therapy.

Erythrocytapheresis using the Haemonetics V50 is technically simple and can be performed in less than 2 hours using one venous access line. A new version of the continuous-flow cell separator (Cobe Spectra; Cobe BCT, Inc, Lakewood, CO), which became available in 1991 for RBC exchange, increases the ease of automated exchange transfusion, shortens the duration of the procedure by

---

### Table 3. Comparison of Annual Net RBC Load Between Erythrocytapheresis and Two Simple Transfusion Protocols

<table>
<thead>
<tr>
<th>Transfusion Protocol</th>
<th>Subject No.</th>
<th>Mean ± 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Erythrocytapheresis (target Hb S &lt;50%)</td>
<td>39.1</td>
<td>32.7</td>
</tr>
<tr>
<td>Conventional simple transfusion (target Hb S &lt;30%)</td>
<td>194.7</td>
<td>112.6</td>
</tr>
<tr>
<td>Modified simple transfusion (target Hb S &lt;50%)</td>
<td>158.4</td>
<td>83.9</td>
</tr>
</tbody>
</table>

For subjects with preapheresis Hb levels less than 8.0 g/dL, each erythrocytapheresis procedure resulted in an increased net RBC load because of an effort to increase post-apheresis Hb levels. The annual iron load in these subjects was higher but still less than one-half to one-third of the iron load with modified simple transfusion. Transfusional iron loading in these subjects could be further reduced if post-apheresis Hb levels were not raised above the preapheresis levels.

The annual donor blood usage with erythrocytapheresis was significantly increased compared with that for simple transfusion. An adult subject who requires erythrocytapheresis every 3 weeks and maintains a pretransfusion Hb level above 8.0 g/dL would need 10 more units of packed-RBC annually in comparison with conventional simple transfusion (Hb S <30%) and 25 more units in comparison with modified simple transfusion (Hb S <50%). Therefore, erythrocytapheresis carries an increased rate of donor exposure compared with that for simple transfusion, thus increasing the risks of transfusion-transmitted infection and alloimmunization against RBC antigens. However, recent estimates of the risk of acquiring hepatitis B, hepatitis C, and human immunodeficiency virus from transfused blood suggest that the benefits of erythrocytapheresis in preventing or delaying iron-induced organ damage outweigh the risks associated with increased donor exposure.

With respect to alloimmunization, Vichinsky et al have reported that the appearance of the first antibody occurred on average after 12 transfusions in 107 patients with sickle cell anemia who received chronic transfusions; 75% of the new antibodies had developed by the twenty-first transfusion. Because patients with stroke may well need life-long transfusion therapy, the overall risk of alloimmunization may not be increased with erythrocytapheresis compared with that for simple transfusion. Nonetheless, the increased donor exposure associated with erythrocytapheresis may promote early onset of alloimmunization, particularly for patients just beginning transfusion therapy. In our study, no subject developed new antibodies while treated with this technique.

### Table 4. Comparison of Annual Donor Packed-RBC Usage Between Erythrocytapheresis and Two Simple Transfusion Protocols

<table>
<thead>
<tr>
<th>Transfusion Protocol</th>
<th>Subject No.</th>
<th>Mean ± 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Erythrocytapheresis (target Hb S &lt;50%)</td>
<td>280.5</td>
<td>258.1</td>
</tr>
<tr>
<td>Conventional simple transfusion (target Hb S &lt;30%)</td>
<td>259.6</td>
<td>147.5</td>
</tr>
<tr>
<td>Modified simple transfusion (target Hb S &lt;50%)</td>
<td>209.6</td>
<td>111.9</td>
</tr>
</tbody>
</table>
nearly one-half, and allows for children weighing less than 20 kg to undergo this therapy. However, all continuous-flow cell separators, including this updated version, require two venous access lines. Inadequate venous access may be an obstacle to long-term erythrocytapheresis therapy in certain subjects, and the additional risks posed by placement of an indwelling venous catheter must be weighed against the benefits of erythrocytapheresis.

In this study, the target pretransfusion Hb S level during erythrocytapheresis therapy was 50%. Although previous studies have suggested that Hb S levels of 50% and 30% are equally effective in preventing recurrent thrombotic stroke, the long-term safety of the higher Hb S level is still unknown. Our preliminary data show that erythrocytapheresis can be used with a target Hb S level of 30% rather than 50% without increasing the RBC load.

Recently, orally effective iron chelators have been under intense investigation, and some are undergoing clinical trials. However, as yet, none is available for regular clinical use. When effective and safe oral chelators become available, compliance with iron chelation therapy may improve. Until that time or until strategies for correcting the underlying hematologic disorder are implemented, every effort should be made to reduce the accumulation of iron in transfusion-dependent subjects. The use of erythrocytapheresis provides a new, safe, and cost-effective approach for delaying or preventing iron overload in subjects with sickle cell disease who require long-term transfusion therapy.

ACKNOWLEDGMENT

We acknowledge the staff in the Transfusion/Apheresis Unit and Blood Bank (Philadelphia, PA) for their contribution to this study. The authors are grateful to Janet Fithian for editorial assistance and to Elizabeth Gil for preparation of this manuscript.

REFERENCES

10. Kim HC, Barrett MS, Presidenedanz H: Modified erythrocytapheresis to retard transfusion-induced iron overload in chronically transfused sickle cell patients. Transfusion 28:245, 1988 (abstr)
30. Leitman SF, Hill EA, Moore RC, Klein HG: Efficacy of
erythrocytapheresis in the treatment of sickle cell disease. Blood 78:199a, 1991 (abstr)


32. McCullough J: The nation’s changing blood supply system. JAMA 269:2239, 1993


34. Charache S: The treatment of sickle cell anemia. Arch Intern Med 133:698, 1974


38. Al-Refaie FN, Wonke B, Hoffbrand AV, Wickens DC, Nortey P, Kontoghiorghes GJ: Efficacy and possible adverse effects of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major. Blood 80:593, 1992
Erythrocytapheresis therapy to reduce iron overload in chronically transfused patients with sickle cell disease

HC Kim, NP Dugan, JH Silber, MB Martin, E Schwartz, K Ohene-Frempong and AR Cohen