Effects of transfusion on rheological properties of blood in sickle cell anemia

K. Jan, S. Usami, and J. A. Smith

The effects of transfusion on the rheological properties of blood in sickle cell anemia were studied in 15 patients. Blood samples were obtained before and after transfusion of normal (hemoglobin AA) packed cells. Blood viscosity was determined with a coaxial cylinder viscometer over a wide range of shear rates. The index of oxygen dependence of blood viscosity (\(\Delta n/\Delta pO_2\)) was calculated as the ratio of viscosity values at low \(pO_2\) (20 mm Hg) and at high \(pO_2\) (100 mm Hg) levels. After transfusion, blood viscosity significantly increased as a result of an elevation of hematocrit. Although transfusion of normal cells into sickle cell anemia patients results in an increased oxygen content of blood and a decreased oxygen dependence of blood viscosity, an elevation of hematocrit value beyond 35 per cent may cause a high viscosity state and outweigh the benefits of transfusion. Judicious monitoring of blood viscosity should serve as a guide for blood transfusion in these patients. TRANSFUSION 1982;22:17-20.

In recent years, the rheological properties of sickle cell (SS) blood have been extensively studied. In patients with SS disease, anemia is always a clinical feature and blood transfusion is often given to these patients. As a result of an elevation of hematocrit and in the presence of normal cells (hemoglobin AA) after transfusion, the rheological properties of blood are subject to significant alterations. Only a few studies have been performed to evaluate these alterations and there is a lack of systematic assessment of blood rheology under this condition, including the quantitative roles of oxygen tension, shear rate, hematocrit, and cell deformability.

Studying the effects of hemodilution and hemoconcentration on the rate of oxygen transport to tissues, several investigators introduced the concept of an "optimum hematocrit" for best tissue oxygenation. Sel£ et al. obtained an in vitro optimum hematocrit for SS anemia patients with the use of a cone and plate viscometer. Such information is not available for SS anemia patients receiving blood transfusion. Although transfusion of normal cells is known to be beneficial for SS anemia patients, overtransfusion could result in a hyperviscosity state and be detrimental. The present investigation was designed to study systematically the changes of rheological properties of blood in SS anemia patients after transfusion.

Elucidation of these changes will provide the basic information needed to define the optimum level of hematocrit after blood transfusion in these patients.

Materials and Methods

The patients with SS disease were admitted to Harlem Hospital in New York City and underwent blood transfusion. Blood samples were obtained before and 12 to 24 hours after transfusion of normal red blood cells. Blood was collected anaerobically from a peripheral vein in a 30-ml heparinized syringe containing approximately 0.5 ml of mercury. The mercury in the syringe was used to stir the blood sample. In the procedure of blood sampling, a tourniquet was applied only briefly during venipuncture and removed prior to sampling.

The hematocrit (packed cell volume, PCV) of each sample was determined by centrifuging at 15,000 x gravity for 5 minutes and was corrected for plasma trapping. Red blood cell (RBC) counts were performed in an electronic particle counter (Coulter Electronics, Hialeah, FL) and hemoglobin concentration (Hb) was determined by using the cyanmethemoglobin reagent. Mean corpuscular volume (MCV) was calculated from the measured values of PCV and RBC count. The per cent of hemoglobin S in total hemoglobin was obtained with the use of microzone electrophoresis on cellulose-acetate strips in tris-EDTA-borate buffer.

Total plasma protein concentration of each sample was determined using a refractometer (Carl Zeiss, Inc., Oberkochen, West Germany). Plasma fibrinogen concentration was determined by the method of Ratnoff and Menzie. The plasma protein fractions were analyzed by means of microzone electrophoresis on cellulose acetate strips in barbitalate buffer.

The determination of \(pO_2\) and pH of samples were made in a blood gas analyzer system (Model 213, Instrumentation Laboratories, Lexington, MA) at 37°C. In order to assess the rheological properties of blood at controlled levels of \(pO_2\) e.g., at 20 and 100 mm Hg, a rotary-type tonometer was used. The concentration of CO2 in the gas mixture was kept at 5.6 per cent to maintain the pH of the sample at normal levels.

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approximately 7.4. The percentages of O₂ and N₂ in the gas mixture were varied to obtain the desired levels with a gas mixture device (Model 208-01 and -02, Instrumentation Laboratories, Lexington, MA). After a blood sample or RBC suspension has been equilibrated with the gas mixture, it was drawn anaerobically into a syringe for PO₂ determination and for rheological measurements.

A coaxial cylinder viscometer was used for measuring blood viscosity. The operation principle of this viscometer has been described elsewhere.\(^*\) The viscosity was determined at 37°C over a shear rate range of 208 to 0.05 sec\(^{-1}\). Measurements were made immediately after the blood sample was obtained from the patient. The results were compared with those obtained from healthy normal hemoglobin AA controls without adjustment of PCV. To assess the degree of oxygen dependence of blood viscosity (ηO₂), the viscosity was also determined with the PO₂ of blood adjusted to 20 and 100 mm Hg by the use of the tonometer. The ηO₂ at a given shear rate was calculated as:

\[
\eta_{O_2} = \frac{\text{viscosity of blood at PO}_2 = 20 \text{ mm Hg}}{\text{viscosity of blood at PO}_2 = 100 \text{ mm Hg}}
\]

The study was performed on 15 patients with SS disease. Nine were men and six were women. The mean age was 26.5 years (range, 15–43). Among these patients, blood transfusion was given to nine for elective surgical procedures, three following cerebrovascular accidents, two for postpartum bleeding, and one for an aplastic crisis. The amount of transfusion averaged two units (range 1–3) of red blood cells.

**Results**

Both the PO₂ and the PCV of the posttransfusion blood samples were significantly higher than those of the pretransfusion samples (Table 1). The relationship between PO₂ and PCV in the blood samples is shown in Figure 1. The PO₂ of blood samples progressively increased with an elevation of PCV up to PCV values between 30 and 35 percent, beyond which further increases in PCV resulted in a reduction of PO₂.

Viscometric measurements of blood samples showed a significant increase in blood viscosity after transfusion (Fig. 2). In comparison with viscosity data obtained from normal hemoglobin AA controls (Hct = 42.6 ± 3.7%), two patients had abnormally high blood viscosities before transfusion. Both of these patients had a pretransfusion PCV of over 30 percent. After transfusion, blood hyperviscosity was noted in the six patients whose PCV rose above 35 percent (Fig. 2). The plasma viscosity, on the other hand, was only slightly elevated after transfusion (Table 1).

The oxygen dependence of blood viscosity (ηO₂) was significantly reduced after transfusion at high shear rates, e.g., above 1 sec\(^{-1}\) (Table 2). The ηO₂ values at lower shear rates were not significantly affected by transfusion.

**Discussion**

Recent developments in blood rheology have shed considerable light on our knowledge of circulatory pathophysiology.\(^{6,13,14}\) The rate of oxygen transport to tissue is determined by the product of the oxygen content of blood and the rate of blood flow.\(^13\) Transfusion results in an elevation of PCV which increases oxygen content of blood on the one hand, and increases blood viscosity on the other. The latter causes a reduction of blood flow.\(^14\) As a result of these two opposing effects of PCV variations on oxygen transport, many investigators have postulated and confirmed the existence of an optimum hematocrit or a range of optimum hematocrits for tissue oxygenation.\(^14\) Under these hypotheses, two rheological problems should be considered in patients with SS disease. First, as a result of anemia, the oxygen content of blood is abnormally low. Blood transfusion is therefore advocated on some occasions, e.g., surgical procedures. Second, deoxygenation of SS RBC is associated with an elevation of blood viscosity.\(^1,13,15\) The increase in blood viscosity, which results in a reduction of blood flow, leads to further lowering of the oxygen tension. Thus, a self-perpetuating cycle of augmented sickling and increasing viscosity may develop. To understand this abnormal rheology, it is necessary to investigate not only the blood viscosity but also the oxygen dependence of blood viscosity, which reflects the degree of blood viscosity changes in response to deoxygenation in the body.

The viscosity of whole blood is determined by hematocrit, plasma viscosity, cell aggregation, and cell deformation.\(^6,13\) Our studies have shown that plasma viscosity does not contribute to the viscometric changes in transfusion (Table 1). The non-Newtonian behavior of blood, i.e., the shear dependent behavior of blood viscosity (Table 2), is primarily due to cell aggregation and cell deformation.\(^13\) As RBC are subjected to shearing, they tend to deform and orient with the flow lines, resulting in a lowering of blood viscosity. The occurrence of RBC aggregation at low shear rates, e.g., below 1 sec\(^{-1}\), causes an increase in blood viscosity and is a predominant rheological factor at low shear rates.

### Table 1. Effect of Transfusion of Normal Red Cells on Blood Gas and Hematological Data in Sickle Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>Pretransfusion Mean ± SD</th>
<th>Posttransfusion Mean ± SD</th>
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</thead>
<tbody>
<tr>
<td>PO₂ (mm Hg)*</td>
<td>32.9 ± 4.8</td>
<td>37.2 ± 4.8</td>
</tr>
<tr>
<td>PCV (%)(^*)</td>
<td>32.7 ± 5.8</td>
<td>33.5 ± 5.9</td>
</tr>
<tr>
<td>MCV (μm(^3))</td>
<td>86.0 ± 12.7</td>
<td>86.8 ± 4.9</td>
</tr>
<tr>
<td>HB S concentration (%)(*)</td>
<td>&gt;95</td>
<td>70.1 ± 14.5</td>
</tr>
<tr>
<td>Plasma viscosity (cP)</td>
<td>1.46 ± 0.13</td>
<td>1.51 ± 0.14</td>
</tr>
<tr>
<td>Plasma proteins (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.69 ± 0.65</td>
<td>7.40 ± 0.58</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.41 ± 0.68</td>
<td>3.19 ± 0.75</td>
</tr>
<tr>
<td>α₁-globulin</td>
<td>0.29 ± 0.10</td>
<td>0.33 ± 0.18</td>
</tr>
<tr>
<td>α₂-globulin</td>
<td>0.49 ± 0.29</td>
<td>0.56 ± 0.13</td>
</tr>
<tr>
<td>β-globulin</td>
<td>0.81 ± 0.15</td>
<td>0.78 ± 0.10</td>
</tr>
<tr>
<td>γ-globulin</td>
<td>2.28 ± 0.26</td>
<td>2.10 ± 0.61</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.395 ± 0.108</td>
<td>0.447 ± 0.118</td>
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</table>

* Comparison of pretransfusion and posttransfusion data by Student t test: p < 0.05.
The abnormal rheological properties of SS blood are attributable to a decrease in the deformability of RBC in response to deoxygenation, a behavior not seen in normal blood. The oxygen dependence of blood viscosity ($\eta_o$) especially at high shear rates, reflects the reduction in SS RBC deformability following a decrease of pO$_2$ from 100 to 20 mm Hg. After transfusion of normal cells, the oxygen dependence of blood viscosity significantly decreased at shear rates higher than 1 sec$^{-1}$ (Table 2). These results indicate that the mixed population of SS and normal RBC following transfusion showed an improved deformational behavior as compared with the pure SS RBC studied prior to transfusion.

The transfusion of blood resulted in a significant increase in blood viscosity due to an elevation of PCV. For a given PCV, the viscosity of the posttransfusion blood samples is lower than that of pure SS blood, but is higher than that of normal blood. If one takes viscosity values of normal blood as controls, transfusion to PCV values greater than 35 per cent in SS patients may result in a significant elevation of blood viscosity above the controls. Such an increase in blood viscosity after transfusion may cause a detrimental decrease in blood flow and outweigh the benefits of the improved oxygen content and the decreased oxygen dependence of the blood.

Thorling and Erslev, with the use of mouse pneumoperitoneum and rat skin pockets, demonstrated that the peak values of pO$_2$ existed at PCV of 45 per cent for normovolemia and 55 per cent for hypovolemia. These hematocrit values correspond to the optimum hematocrits in these animals. In the present investigation, an analysis of pO$_2$ in the forearm venous blood before and after transfusion shows that the maximum venous pO$_2$ is obtained at PCV values approximately between 30 and 35 per cent, beyond which further increases in PCV result in a reduction of pO$_2$. The latter is probably due to a progressive reduction of blood flow in tissues from elevation of blood viscosity. The range of optimum hematocrit after transfusion is interestingly in good agreement with the value predicted by viscosity studies. Judicious monitoring of the blood viscosity, therefore, should serve as a useful guide for blood transfusion in patients with SS disease. If a viscometer is not available, blood transfusion beyond a PCV value of 35 per cent should be avoided. For patients with a relatively high pretransfusion value of PCV, e.g., above 25 per cent, exchange blood transfusion or partial exchange transfusion, with the removal of a certain amount of SS blood, may provide advantages over simple transfusion in that the increase in PCV is associated with a further decrease in SS RBC population and hence a lesser increase of blood viscosity.

The oxygen dependence of the blood.

Table 2. Effect of Transfusion of Normal Red Cells on Oxygen Dependence of Blood Viscosity ($\eta_o$ in Sickle Cell Disease)

<table>
<thead>
<tr>
<th>Shear Rates (sec$^{-1}$)</th>
<th>$\eta_o$ (Mean ± SD)$^\dagger$</th>
<th>Pretransfusion</th>
<th>Posttransfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>208*</td>
<td>1.53 ± 0.36</td>
<td>1.23 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>104*</td>
<td>1.49 ± 0.26</td>
<td>1.20 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>52*</td>
<td>1.46 ± 0.22</td>
<td>1.20 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>5.2*</td>
<td>1.36 ± 0.17</td>
<td>1.14 ± 0.22</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>1.11 ± 0.04</td>
<td>1.13 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>1.08 ± 0.27</td>
<td>1.11 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>1.37 ± 0.50</td>
<td>1.39 ± 0.23</td>
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</tbody>
</table>

$^\dagger$ Comparison of pretransfusion and posttransfusion data by Student $t$ test; $P < 0.05$.

$^*$ $\eta_o$ values of normal (hemoglobin AA) blood were 1.00 at all shear rates.
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References


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