Painful sickle cell crises precipitated by stopping prophylactic exchange transfusions

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SUMMARY A patient with homozygous sickle cell disease showed a reduced incidence of painful crises as a result of regular exchange transfusion, but on three occasions when transfusion treatment was interrupted, a painful crisis occurred. Onset of painful crisis was associated with raised packed cell volume (PCV) or percentage of haemoglobin S (HbS%), or both. Measurement of whole blood viscosity using *in vitro* mixtures of blood group compatible normal (AA) and sickle (SS) cells showed that above an HbS of 25% any increase in PCV caused a disproportionate increase in whole blood viscosity. These clinical observations and laboratory data suggest that when regular exchange transfusions are terminated both HbS% and PCV should be carefully monitored. Prophylactic venesection should be considered for patients who maintain their PCV after transfusion as HbS% rises.

The viscosity of whole blood is determined by its packed cell volume (PCV), plasma viscosity, and the deformability and aggregation of its erythrocytes. The rheological contribution of each of these components to whole blood viscosity can be measured individually,^{1,2} but all of them must be taken into account in clinical studies as a change in one may offset or add to the effects of another. This is particularly important in rheological studies of sickle cell disease. In the steady state of sickle cell disease the viscosity of oxygenated sickle (SS) blood is lower than that in normal (AA) controls because the rheological benefit of anaemia³ more than compensates for the poor deformability of SS cells. Exchange transfusions will lower the whole blood viscosity of patients with sickle cell disease (assuming no change in PCV) as the transfused AA erythrocytes are more deformable.⁴ If, however, the PCV is allowed to increase whole blood viscosity will consequently rise above normal.⁵ For this reason, exchange, rather than top up, transfusion is often preferred.⁶

On stopping long term prophylactic transfusions in sickle cell disease, it is assumed that the rheological effect of the rising percentage of haemoglobin S (HbS%) is offset by the falling PCV, so that whole blood viscosity does not increase. In some cases, how-

ever, endogenous erythropoiesis may not be fully suppressed by the transfusion programme. Such patients may maintain their post-transfusion PCV for several weeks and thus are at rheological risk of vascular occlusion as their HbS% increases during this transitional period. This rheological hazard of stopping prophylactic transfusions has not been adequately documented.

Case reports

A 24 year old male graduate with homozygous sickle cell disease had suffered frequent and severe painful crises (12 in 27 months), causing considerable disruption to his school and college studies. He was therefore started on prophylactic exchange transfusions from December 1983. Having successfully completed undergraduate studies in June 1985, transfusions were stopped. By this time his serum ferritin concentration had increased to 3188 µg/l (reference range 15–300). In August 1985, 10 weeks after the last transfusion, he was admitted in painful crisis affecting the right shoulder, elbow, and knee. Despite analgesics and intravenous fluids he failed to improve. Exchange transfusions were carried out on days four and seven after which he recovered quickly. Having relapsed so soon after discontinuation of regular transfusions, these were restarted on a prophylactic basis for a further six months.

During 18 months of prophylactic transfusions

(December 1983 to June 1985), the patient required five admissions for painful crises (table 1). Two of these episodes (crises 2 and 4) occurred when transfusion was inadvertently delayed, two others (crises 1 and 3) occurred when both HbS% and PCV were relatively high, and one (crisis 5) was precipitated by staphylococcal pneumonia. The data suggested that a crisis was more likely to occur when HbS% or PCV, or both, were raised and led us to investigate the individual and combined effects of HbS% and PCV on whole blood viscosity in vitro.

Methods

Venous blood from two healthy AA subjects and two SS patients in the steady state was anticoagulated with K₂EDTA (1.5 mg/ml blood) and tested within four hours of venepuncture. The HbS% was obtained using paper electrophoresis and elution⁷ or agarose gel (pH 8.6) electrophoresis and scanning densitometry (Beckman Paragon Electrophoresis System, Beckman Instruments, Brea, California, USA). Packed cell volumes were determined by micro-haematocrit centrifugation of oxygenated red cells for 10 minutes at 13000 g (Hawksley and Sons Ltd, Lancing, Sussex).

ABO and Rhesus matched AA and SS blood samples were tested for compatibility at room temperature using a low ionic strength saline two way cross match. Whole blood viscosity was measured at 25°C and ambient oxygen tension using a Contraves low shear 30 rheometer (Contraves Industrial Products Ltd, Ruislip, Middlesex) at a high shear rate of 128.5 seconds⁻¹.

Mixtures of compatible AA and oxygenated SS whole blood were made to give final concentrations of 0, 25, 50, 75, and 100% HbS. For each HbS%, samples of differing PCV (range 0.20–0.70) were obtained by the addition or removal of plasma. The viscosity of each sample was then measured and a regression line of log viscosity against PCV drawn for each HbS%.

Table 1 Clinical and haematological details at time of hospital admission for painful crisis (crises 1–5 during, and crisis 6 after, 18 months of prophylactic exchange transfusions) compared with those obtained in asymptomatic steady state value

Clinical details	HbS%	PCV
Mean (SEM) pretransfusion value when patient asymptomatic (n = 10)	47.1 (3.3)	0.34 (0.001)
Crisis 1	61	0.37
Crisis 2—transfusion delay	—	0.31
Crisis 3	50	0.39
Crisis 4—transfusion delay	60	0.31
Crisis 5—staphylococcal pneumonia	53	0.32
Crisis 6—transfusion programme stopped	59	0.33

Using the five regression lines, viscosity values at PCVs of 0.15, 0.25, 0.35, and 0.45 were estimated for each HbS%. As values for whole blood viscosity are commonly expressed in relation to a PCV of 0.45, the viscosity value for AA blood (0% HbS) at a PCV of 0.45 was assigned an arbitrary reference value of 100%, and all other viscosity values were expressed as a percentage of this value.

Results

The regression line relating log viscosity to PCV was steeper for SS (slope 1.512) than for AA (slope 1.323) blood so that, at the same PCV, the viscosity of SS blood was always higher (figure). Table 2 shows the effects of variation in HbS% and PCV on whole blood viscosity. As the observed regression lines of log viscosity against PCV for each HbS% (25, 50, and 75%) were found to overlie the lines predicted from the proportional summation of appropriate values from the 0% (AA) and 100% (SS) regression lines, we were able to construct a table showing the predicted effect on whole blood viscosity over a wider range of HbS% values (table 1). As the HbS% increased a given rise in PCV had a larger effect on whole blood viscosity.

Figure Regression lines relating log whole blood viscosity to packed cell volume for one SS ($y = 1.512x + 0.232$) and one AA ($y = 1.323x + 0.213$) sample.

Table 2 Observed and predicted effects of PCV and HbS% on whole blood viscosity at ambient oxygen tension and high shear*

	0.15	0.25	0.35	0.45
Observed:				
HbS%—0 (AA)	44.0	57.7	76.0	100.0
25	41.5	56.1	76.2	103.4
50	46.4	64.0	88.9	123.4
75	48.8	66.9	91.6	125.3
100 (SS)	46.3	65.5	92.7	131.0
Predicted:				
HbS%—25	44.6	59.8	80.2	107.8
30	44.7	60.1	81.0	109.3
35	44.8	60.5	81.8	111.0
40	44.9	60.9	82.7	112.6
45	45.1	61.3	83.4	114.1
50	45.2	61.6	84.2	115.5
55	45.3	62.1	85.2	117.3
60	45.4	62.4	86.0	118.6
65	45.5	62.8	87.3	120.4
70	45.6	63.2	87.7	121.9
75	45.7	63.6	88.6	123.5

*Viscosity results (means for two experiments) expressed as percentage of 100% value assigned to AA blood at PCV of 0.45.

Discussion

Whole blood viscosity, because of its dependence on PCV, is of particular value in monitoring the rheological effects of exchange transfusion in sickle cell disease.⁸ The effect of PCV on whole blood viscosity is well documented for both AA⁹ and SS¹⁰ blood, and the beneficial effect of dilution with AA cells on the rheology of SS cells has been shown in vitro^{4,5,11} and borne out by clinical observations.^{12,13} An increase in PCV and a decrease in HbS% have opposing rheological effects on whole blood viscosity, but the rheological balance between the two variables has not been formally investigated.

Using in vitro mixtures of varying HbS%, we have shown the separate and combined effects of PCV and HbS% on whole blood viscosity at ambient oxygen tension. As the HbS concentration increased there was a progressive rise in whole blood viscosity, the effect being more pronounced at higher PCV values. All whole blood viscosity values (0–100% HbS) at a PCV of 0.35 were below that of AA blood at a PCV of 0.45, emphasising the major influence of PCV on whole blood viscosity for oxygenated samples. On deoxygenation, however, the whole blood viscosity of SS blood increases disproportionately,³ with the HbS% then becoming the major determinant of whole blood viscosity. Thus in vivo the combination of a relatively high HbS% and PCV is particularly detrimental to blood rheology in patients with sickle cell disease.

Although a rheologically "critical" value for whole blood viscosity in sickle cell disease has not been defined, most clinicians perform exchange, rather than top up, transfusions to avoid a rise in PCV. A long term reduction of HbS% by this means is

accepted management for patients with sickle cell disease who experience cerebrovascular accidents, episodes of chest syndrome, or repeated painful crises.⁶ The problem is when to stop treatment, as there have been reports of cerebral vaso-occlusive episodes¹⁴ occurring when transfusions have ceased, and long term transfusions may lead to iron overload¹⁵ unless chelation treatment is also given. Many patients are unwilling to stop transfusions, however, for fear of recurrence of painful crises. If a painful crisis does occur as treatment is withdrawn this may lead to reinstitution of transfusions and reinforce patient dependence. Careful monitoring of both PCV and HbS% at the time transfusions are discontinued is therefore recommended. If the rising HbS% is not sufficiently offset by a fall in PCV then limited venesection will prevent a rise in whole blood viscosity, which may otherwise precipitate painful crisis. This approach should allow the patient to be successfully and uneventfully weaned off treatment by transfusion.

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