Vasoconstrictor-Induced Hypertension Following Multiple Blood Transfusions in Children With Congenital Hemolytic Anemia

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Introduction. The mechanism by which blood transfusion increases blood pressure in a substantial proportion of patients with congenital hemolytic anemia is unknown. Vascular endothelium dysfunction and increased endogenous vasoactive substances have been postulated in the pathogenesis of hypertension following multiple blood transfusions. The present study was undertaken to test the hypothesis whether increased circulating vasoconstrictors following blood transfusions, if documented, is a potent modulator of hypertension in patients with congenital anemia.

Materials and Methods. Four children with congenital hemolytic anemia developed severe hypertension and convulsions 2 to 4 days after they received multiple blood transfusions. None had a history of prior hypertension, kidney disease or seizures before the blood transfusion. Baseline blood and urine samples were obtained for routine renal function studies. Blood samples were also drawn during and 2 weeks after the clinical events for determination of epinephrine, norepinephrine, dopamine, and plasma renin activity.

Results. Kidney function was normal in all the 4 patients. All had elevated plasma renin activity and increased blood epinephrine, norepinephrine, and dopamine concentrations during hypertensive crises. Hypertension responded to antihypertensive drugs with the patients remaining normotensive 3 to 6 days after commencing therapy. All recovered without further seizures. The elevated plasma renin activity, epinephrine, norepinephrine, and dopamine levels returned to reference levels 2 weeks after completion of the last blood transfusion.

Conclusions. These data suggest that increased activity of vasoconstrictors in the recipient plasma may be responsible for the development of hypertension after multiple blood transfusions.

INTRODUCTION
Thalassemia and sickle-cell disease (SCD) represent the most common forms of hereditary hemoglobinopathy. A syndrome of hypertension, convulsions, and cerebral hemorrhage has been reported in thalassemic and SCD patients after multiple blood transfusions. Increased vascular responsiveness to endogenous vasoconstrictors occurring in association with multiple blood transfusions has been suggested to contribute significantly to this syndrome. Despite these observations, it remains uncertain whether the recipient’s plasma contains sufficient bioactive vasoconstrictors to cause significant increases in the blood pressure (BP) after blood transfusions.

While reviewing the literature on hypertension,
it became apparent to the author that episodes of severe hypertension associated with convulsions and sometimes cerebral hemorrhage were common during the period of rapid blood transfusions in patients with congenital hemolytic anemia.\(^1\)\(^-\)\(^9\) While the literature has accumulated on hypertension, there is no published report characterizing the mechanism of hypertension after rapid blood transfusions in these patients. The present prospective study was designed to determine whether there is any causal relationship between the circulating vasoconstrictors and the development of hypertension in children with congenital hemolytic anemia following multiple blood transfusions.

**MATERIALS AND METHODS**

Four patients (3 boys and 1 girl; age range, 3 to 14 years) with congenital hemolytic anemia were studied. They received blood transfusions in preparation for splenectomy and/or management of severe anemia. Two of them had beta-thalassemia, 1 had SCD, and 1 had hereditary spherocytosis (Table 1). None of them had a history of previous cardiovascular disease, kidney disease, or seizures, and none had hypertension before blood transfusions. All of the patients had hepatosplenomegaly and retarded growth. The remaining of physical examination was unremarkable.

Blood pressure was measured by auscultation with a calibrated aneroid sphygmomanometer and an appropriately sized cuff in the right arm with the patient in the supine position and arm at heart level. The first and the last Korotokoff sounds were used to determine systolic and diastolic BPs. Three measurements were made, each separated from the next by at least 10 minutes. Hypertension was defined as the average systolic and/or diastolic BP equal to or higher than the 95th percentile for the patient’s sex, age, and height.\(^1\)\(^0\) The mean arterial pressure was defined as the diastolic pressure plus one-third of the pulse pressure (systolic BP – diastolic BP).

Baseline blood and urine samples were obtained for routine kidney function studies. Blood samples were also drawn, in the supine position and with unrestricted salt intake, during and 2 weeks after the hypertension crises for determination of blood epinephrine, norepinephrine, and dopamine levels, and plasma renin activity (PRA). All of the patients underwent computed tomography of the brain, electroencephalography, and cerebrospinal fluid examinations. All imaging and chemical analyses were performed in the hospital diagnostic radiology and clinical laboratory departments, respectively as part of the routine standards of care. Glomerular filtration rate (GFR) was estimated using the Schwartz formula.\(^1\)\(^1\) All of the patients were treated with intravenous infusion of nicardipine (5 mg/h to 10 mg/h) and labetalol (0.1 mg/h to 0.7 mg/h) as required to achieve a systolic and/or diastolic BP goal (< 95 the percentile, corrected for age, sex, and height).\(^1\)\(^0\)

Table 1 and the following provide more detailed and specific information to each studied patient:

**Patient 1**

A 7-year-old boy with beta-thalassemia major was admitted to the hospital because of severe anemia. He was diagnosed as having beta-thalassemia at the age of 1 year. He appeared pale and had delayed skeletal maturation. The spleen was palpable 12 cm below the left costal margin. Serum creatinine concentration was 0.4 mg/dL, and estimated GFR was 117 mL/min/1.73 m\(^2\). He received 1.5 units of packed erythrocytes on 2 successive days. Three days after completion of the last transfusion, he complained of a severe headache and developed an acute episode of hypertension followed by a generalized grand-mal seizure, lasting 3 to 4 minutes.

**Patient 2**

A 6-year-old girl with beta-thalassemia intermedia was admitted with the signs and symptoms of left
middle lobe pneumonia. She was diagnosed as having beta-thalassemia intermedia at the age of 4 years. Serum creatinine concentration was 0.3 mg/dL and estimated GFR was 111 mL/min/1.73 m². Because of severe anemia she received a transfusion of 1 unit of packed erythrocytes on 2 successive days. Two days later, hypertension, headache, and 1 episode of grand-mal seizure lasting for 2 to 3 minutes occurred.

**Patient 3**

A 14-year-old black boy with homozygous SCD was admitted because of acute chest syndrome and transfused with 1.5 units of packed erythrocytes on 2 successive days. Serum creatinine concentration was 0.6 mg/dL and estimated GFR was 119 mL/min/1.73 m². Two days after completion of the last blood transfusion, he complained of severe headaches and developed hypertension complicated with multiple grand-mal seizures lasting for 5 to 8 minutes.

**Patient 4**

A 3-year-old boy with hereditary spherocytosis was transfused with 1 unit of packed erythrocytes on 3 successive days in preparation for splenectomy and management of severe anemia. Serum creatinine concentration was 0.3 mg/dL and estimated GFR was 110 mL/min/1.73 m². Four days after transfusions, a marked increase in BP was observed and he developed generalized seizures lasting 5 to 7 minutes.

**RESULTS**

Summary of the patients' clinical and laboratory data are presented in Table 2. Baseline urinalysis, blood chemistry, and estimated GFR did not reveal any indication of kidney disease in any of the 4 patients. All had elevated PRA and increased blood epinephrine, norepinephrine, and dopamine concentrations during the attack. The elevated BP returned to its normal level after 3 to 6 days of intense antihypertensive therapy. The increased PRA, epinephrine, norepinephrine, and dopamine levels returned to normal values 2 weeks after completion of the last blood transfusion (Figure). No abnormal finding was detected in the computed tomography scan of the brain or the cerebrospinal fluid of the patients. The initial electroencephalography showed mild-to-moderate irregular cerebral bioelectrical activity in all of the 4 patients. All recovered well without further episodes of seizure and had normal electroencephalography findings 4 to 6 weeks following the clinical event.

**DISCUSSION**

A syndrome of hypertension, convulsions, and cerebral hemorrhage has been reported in about 17% of patients with thalassemia and SCD after multiple blood transfusions. Patients reported in this study are similar to those previously reported in the literature in presentation and clinical progress. The 4 patients were not hypertensive before transfusion and did not have a history of previous seizures or any indication of kidney disease or cardiovascular disease. All developed hypertension and convulsions within 2 to 4 days after completion of the last transfusion. The hypertension episode was associated with increased PRA and elevated blood epinephrine, norepinephrine, dopamine concentrations, all of which returned to normal values following the BP control measures (Table 2). One of the patients in the present study had congenital spherocytosis suggesting that transfusion-related hypertension is not unique to SCD and thalassemia.

The rise in BP after blood transfusions was not the result of intravascular volume overload, since the hypertension occurred 1 to 3 days after completion.

<table>
<thead>
<tr>
<th>Patient</th>
<th>BP, mm Hg</th>
<th>Hb, g/dL</th>
<th>PRA, ng/mL/h</th>
<th>Epinephrine, pg/mL</th>
<th>Norepinephrine, pg/mL</th>
<th>Dopamine, pg/mL</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
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<td>8.9</td>
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</table>

*Measurements of BP and Hb were before and after transfusion, while PRA, epinephrine, norepinephrine, and dopamine were measured during hypertension crisis and 2 weeks after the last transfusion. BP indicates blood pressure; Hb, hemoglobin; PRA, plasma renin activity.
Blood levels of epinephrine, norepinephrine, and dopamine, and the mean arterial pressure during the hypertensive crises and at a 2-week follow-up.

of the last transfusion. The circulatory overload usually begins near the end or within 6 hours of the transfusion and the blood volume usually returns to normal within 24 hours of a transfusion in patients with normal kidney function. Thus, it would appear that the hypertension crises in these patients may be caused by vasoactive substances introduced by multiple blood transfusions.

Hypertension crisis was reported in a patient with end-stage renal disease after platelet transfusions in conjunction with erythropoietin therapy. Intracellular concentrations of vasoactive substances are high in normal platelets, and through the mechanism of aggregation, they can be locally released in the peripheral circulation. Therefore, the infusion or release of these substances from aggregated platelets may explain the increase in BP in the recipient after multiple blood transfusions.

The host factors suggested by Wasi and colleagues may also contribute significantly to this syndrome. Life-long severe anemia is common in patients with congenital anemia. Chronic anemia is associated with endogenous overproduction of erythropoietin. Increased synthesis and release of endothelin-1 are known to be the primary effect of erythropoietin in the endothelium. It is likely that these changes
in endothelial function may impair vascular responsiveness to endogenous vasoconstrictors, such as epinephrine, norepinephrine, dopamine, and angiotensin II.\textsuperscript{12,13} Furthermore, increase in local synthesis and secretion of endothelin-1 may amplify the effects of other potential vasoconstrictors, such as serotonin.\textsuperscript{9} In addition, the interaction of platelets with endothelin-1 could lead to the release of other substances from aggregated platelets such as transforming growth factor-beta, platelet-derived growth factor, and fibroblast growth factor, which are known to enhance endothelin-1 synthesis and promote the proliferation of the endothelial cells.\textsuperscript{14} The endothelium dysfunction may in turn impair vascular responsiveness to the vasoconstrictor effects provided by blood transfusion.\textsuperscript{13,15} It has been suggested that iron overload and a sudden increase in hemoglobin concentration in patients with chronic anemia who have adapted to survive on low hemoglobin concentrations may also predispose to this syndrome.\textsuperscript{16,17}

CONCLUSIONS
Transfusion-related hypertension is mediated by endogenous vasoconstrictors occurring in association with multiple blood transfusions. The possibility of a fatal outcome when a patient with chronic anemia is intensely transfused must be recognized. Thus, the benefits of transfusion should always be balanced against any possible risks. Blood pressure monitoring and prompt antihypertensive therapy may be lifesaving in such situations.

CONFLICT OF INTEREST
None declared.

REFERENCES

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