Hemoglobin and 2,3-Diphosphoglycerate Levels in Transfused Dialysis Patients with Myocardial Infarction*†‡

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ABSTRACT

Thirty frequently transfused patients on long term hemodialysis were studied and a similar number of age and sex-matched patients who were infrequently transfused were used as a control group to ascertain the influence of a previous myocardial infarction (MI) on transfusion requirements. The frequency of previous MI on electrocardiogram (ECG) in the transfused and control groups was similar (40 percent and 37 percent, respectively). In frequently transfused dialysis patients with MI, the hemoglobin level (transfusion trigger) at which these patients were transfused was higher than that of frequently transfused patients without MI (8.3 ± 1.5 g per dl vs. 6.9 ± 1 g per dl, p < 0.01) which indicated that patients without MI tolerated a greater degree of anemia than those with MI. The 2,3-diphosphoglycerate (2,3-DPG) levels were significantly elevated in all transfused patients when compared to matched controls. However, levels of 2,3-DPG were significantly higher in MI patients receiving frequent transfusions than in other transfused patients, suggesting oxygen demands may not have been fully met despite the frequent transfusions. The results suggest levels of 2,3-DPG deserve further study in relation to the adequacy of tissue oxygenation in anemic dialysis patients.

* Supported by the U.S. Navy (Office of Naval Research Contract N0001488-C-0118) with the funds provided by the Naval Medical Research and Development Command.
† The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.
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Introduction

Cardiac output is the major determinate of oxygen delivery when arterial oxygen content is normal. If oxygen content falls because of a reduction in hemoglobin, an increase in cardiac output is the major compensatory mechanism. Myocardial infarction (MI) is the most common cause of chronic impairment in cardiac output. In a chronically anemic population, transfusion requirements may be anticipated to be greater when cardiac output is reduced. Patients on long term hemodialysis are chronically anemic owing to depressed levels of erythropoietin (EPO). They often require chronic transfusion support although the level of transfusion support varies widely in this population, and, with the advent of EPO, transfusion therapy has been much reduced. Patients on long term hemodialysis also have a high incidence of myocardial infarction. Thus, patients on long term hemodialysis provide a suitable population in which to study the influence of myocardial infarction on pretransfusion hemoglobin levels (transfusion trigger).

It has been previously reported by us that there is a group of intensely transfused dialysis patients (ITD) which is essentially transfusion dependent. The primary indication for transfusion in this group was easy fatiguability. In the present study, the ITD population was compared with a control population of patients on dialysis who were not intensely transfused with respect to the presence of MI in the two groups. In this group of patients, not previously treated with EPO, ways were sought to determine how a previous MI in this setting influences transfusion practice and hemoglobin requirements.

Methods

I. DIALYSIS POPULATION

Sixty patients receiving hemodialysis at the Artificial Kidney Center of Rhode Island (AKC) were studied. The first 30 patients selected had received five or more transfusions within the previous six months. These patients were designated intensely transfused dialysis patients (ITD). The remaining 30 patients received no transfusions during this time and were designated as dialysis controls (DC). The dialysis controls were individually matched to the ITD group by sex, age, and the number of months on dialysis. The standard treatment for patients on dialysis at the AKC is a program of three dialysis periods weekly. Study group and control patients were comparably dialyzed.

II. SAMPLE COLLECTION

Blood for analysis was obtained from the patients at the AKC prior to the administration of heparin, transfusion, or hemodialysis treatment.

III. HEMATOLOGIC MEASUREMENTS

Complete blood counts (CBC) were performed.* Reticulocyte counts were done by a standard new methylene blue dye method. The absolute reticulocyte count was determined by multiplying the RBC count by the percent of reticulocytes.

IV. BIOCHEMICAL MEASUREMENTS

Erythropoietin levels were measured in a competitive radioimmunoassay.† Red blood cell adenosine triphosphate (ATP), 2,3-DPG, and inorganic phosphorus were assayed using neutralized perchloric acid extracts of heparinized whole blood. Both ATP and 2,3-DPG levels were measured fluorometrically. Inorganic phosphorus was also measured.‡

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* Coulter Counter Model S.
† SmithKline Beecham Laboratories.
‡ COBAS chemistry instrument using Roche reagent for inorganic phosphorus.
TABLE I

Characteristics of Intensely Transfused Dialysis Patients and Infrequently Transfused Dialysis Control Populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intensely Transfused Dialysis</th>
<th>Dialysis Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ml No Ml All</td>
<td>Ml No Ml All</td>
</tr>
<tr>
<td>M/F</td>
<td>6/6 5/13 11/19</td>
<td>2/9 9/10 11/19</td>
</tr>
<tr>
<td>Number</td>
<td>12(40%) 18(60%) 30</td>
<td>11(36.7%) 19(63.3%) 30</td>
</tr>
<tr>
<td>Age</td>
<td>55.8 ± 18.0 52.2 ± 21.6 53.7 ± 20.3</td>
<td>62.1 ± 18.5 52.3 ± 17 55.9 ± 17.9</td>
</tr>
<tr>
<td>Months on Dialysis</td>
<td>36.8 ± 31.2 35.6 ± 33.2 36 ± 31.9</td>
<td>43.1 ± 36.2 39.1 ± 39.3 40.5 ± 37.6</td>
</tr>
<tr>
<td>Units Transfused</td>
<td>115.8 ± 148.2 69.8 ± 54.6 88.2 ± 103a</td>
<td>7 ± 5b 2.7 ± 3.9b 4.3 ± 4.7a</td>
</tr>
<tr>
<td>Median Number of Units</td>
<td>250 108 249</td>
<td>9 7 9</td>
</tr>
</tbody>
</table>

Ml = myocardial infarction  a p = <0.001  b p = <0.05

V. ELECTROCARDIOGRAM

Routine electrocardiograms (ECG) were obtained on all patients. The ECGs were classified into two groups, those with ECG evidence of MI and those without such evidence. The ECG interpretation was performed blindly by a cardiologist who was otherwise not involved in the study.§

VI. STATISTICAL ANALYSIS

The mean and standard deviation (SD) were reported for each group. The means of the two groups were compared by using the nonpaired t-test. A p value of <0.05 was considered significant.

Results

There were no significant differences between the groups in the parameters of age, sex, and months on long term hemodialysis (table I), but the two groups, as expected, differed significantly (p < 0.001) in terms of the total lifetime number of blood transfusions each had received (88.2 ± 103 vs. 4.3 ± 4.7 units) and their degree of iron overload as reflected in ferritin levels (table II).

In table II are also shown a comparison of the hematologic parameters of the ITD and the infrequently transfused dialysis control population as well as a comparison of both groups with normal values. These data are further subdivided as to the presence of MI in these groups. There were significant overall differences in the red blood cell counts and other red cell parameters for ITD versus DC with the mean hematocrit of ITD and DC being 22.2 ± 4.2 vs. 25.9 ± 5 relative to normal (p < 0.001).

In patients who are not frequently transfused, there was no significant difference between the hemoglobin levels of those with MI versus those without MI (8.3 ± 1.2 vs. 8.7 ± 1.8). In contrast, there was a significant difference in the pretransfusion hemoglobin of frequently transfused dialysis patients with MI versus frequently transfused patients without MI (8.3 ± 1.6 vs. 6.9 ± 1.1, p < 0.01) (figure 1).

The level of 2,3-DPG in ITD was greater than the level of 2,3-DPG of either normals or DC (table III). There was a significant increase in levels of 2,3-

§ Dr. Nicholas Ruocco, Boston University School of Medicine.
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI</td>
<td>No MI</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>24.6 ± 4.6a</td>
<td>20.6 ± 3.1a</td>
</tr>
<tr>
<td>Reticulocytes x 10^6/μl</td>
<td>0.068 ± 0.03</td>
<td>0.052 ± 0.04</td>
</tr>
<tr>
<td>Erythropoietin, mIU/ml</td>
<td>13.3 ± 5.7</td>
<td>11.6 ± 7.1</td>
</tr>
<tr>
<td>Ferritin, ng/ml</td>
<td>4278 ± 4690</td>
<td>2004 ± 1876</td>
</tr>
</tbody>
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*Ml = myocardial infarction  
^a,b p < 0.01

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<td>N</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>2,3 DPG μM/gm Hb</td>
<td>20.2 ± 6.6a</td>
<td>15.4 ± 3.5a</td>
</tr>
<tr>
<td>ATP, μM/gm Hb</td>
<td>5.9 ± 1.2</td>
<td>5.8 ± 2.4</td>
</tr>
<tr>
<td>Inorganic PO₄, mg/dl</td>
<td>4.9 ± 1.5</td>
<td>4.4 ± 2.3</td>
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*Ml = myocardial infarction  
^a,b p < 0.05
HEMOGLOBIN AND 2,3-DPG LEVELS IN TRANSFUSED DIALYSIS PATIENTS WITH MI

Discussion

In the absence of abnormalities of electrolytes or calcium, the resting ECG is usually a reliable means to diagnose myocardial infarction in dialysis patients. In the present study, intensely transfused dialysis patients (ITD) were not more likely than their matched, less intensely transfused dialysis control patients to have had an MI (12 of 30 vs. 11 of 30) as demonstrated by the resting electrocardiogram. Myocardial infarction in the ITD was associated with significantly higher pre-transfusion hemoglobin level (p < 0.01) at the time MI patients required transfusion than other intensely transfused dialysis patients. These findings suggest oxygen delivery may be more impaired in ITD patients with MI than is oxygen delivery in ITD patients without MI. The high levels of ferritin (table II) were in a range consistent with transfusion related hemosiderosis, and a vicious cycle could have developed in the ITD patients with MI as cardiac iron deposition further worsened cardiac function.

The influence of hemoglobin levels on transfusion practice has not previously been extensively studied in relation to the transfusion requirements of anemic patients. Neff et al studied a large group of patients being maintained on long term hemodialysis when their clinical condition was stable. The cardiac index of these patients was significantly elevated. A subset of patients was studied before and after progressive blood transfusion to hematocrits above 40, and there was a clear inverse correlation between cardiac index and hematocrit in these patients (r = 0.76, p < 0.01). A normal level of cardiac index was not reached in most patients until a hematocrit of 30 percent was achieved, which was above the transfusion hemoglobin levels of most of the patients studied by us. From the study of Neff et al, a relative increase in cardiac index was probably present in most of the patients studied by us. Thus, it may be that the reason an MI was associated with an increased higher pre-transfusion hemoglobin level than matched transfused controls without MI was related to a relatively inadequate increase in cardiac index in the MI group and consequent inadequate oxygen delivery.
Previous studies\textsuperscript{2,3,9} have shown that a spectrum of chronic hemodynamic abnormalities may be present singly or in different combinations in the post-infarction patient. These disorders include localized abnormalities of ventricular contraction, mitral regurgitation and low ejection fraction.\textsuperscript{2} A high resting ventricular filling pressure, low cardiac index, and an increased end-diastolic volume are commonly associated with these conditions. Moraski et al\textsuperscript{9} concluded that the left ventricular ejection fraction (LVEF) is the most sensitive measurement of left ventricular function following MI. Subsequently Lai et al\textsuperscript{6} showed that in a randomly selected dialysis population, LVEF was less than 50 percent in seven of 37 subjects (19 percent). Studies of LVEF in relation to pre-transfusion hemoglobin levels in the ITD population would be of interest to define further the contribution of decreased left ventricular function to the hemoglobin requirements of these patients.

In the present study, ITD patients with MI showed indirect biochemical evidence of a deficiency in oxygen delivery, since their mean level of 2,3-DPG was significantly increased over transfused controls (table III) despite their higher hemoglobin levels at the time of transfusion. Levels of 2,3-DPG in the other group were not elevated as high as that reported in other chronic anemias.\textsuperscript{7,12} probably because of inhibition of synthesis of 2,3-DPG by chronic acidosis.\textsuperscript{7} The work of Oski et al\textsuperscript{12} suggests that individuals with higher levels of 2,3-DPG have a less increased cardiac index in response to workload in contrast to patients with lower levels of 2,3-DPG in whom there is a greater need for cardiac compensation. Thus, increased levels of 2,3-DPG may have offset to some degree any left ventricular dysfunction present in the transfused MI patients. However, control of synthesis of 2,3-DPG in patients on long term dialysis is greatly influenced by pH as well as the complex and possibly opposing effect of respiratory alkalosis, metabolic acidosis, and phosphate levels.\textsuperscript{7} Therefore, the role of increased levels of 2,3-DPG in improving oxygen delivery in ITD patients with MI will need more comprehensive study before any firm conclusion can be reached regarding the relative increase in levels of 2,3-DPG noted in regularly transfused MI patients.

In summary, it has been demonstrated by the present authors that when anemic MI patients require transfusion, they are transfused at higher pretransfusion hemoglobin levels (transfusion trigger) than patients without MI. Their relatively increased levels of 2,3-DPG are suggestive that inadequate oxygen delivery may be the cause of the increased transfusion requirements. The ability of red blood cell levels of 2,3-DPG to predict hypoxia in this population deserves further study.

\textit{Acknowledgments}

The authors gratefully acknowledge the help of Dr. John Pezzullo and Ms. Linda Pivacek in the analysis of data. Thanks are extended to Judy Fuller for secretarial assistance. Special thanks are given to the patients at the Artificial Kidney Center of Rhode Island for their enthusiastic participation in this study.

\textit{References}


