The Effect of 6% Hydroxyethyl Starch and Desmopressin Infusion on Von Willebrand Factor: Ristocetin Cofactor Activity*

JOHN LAZARCHICK, M.D.†
and JOANNE M. CONROY, M.D.‡

†Department of Pathology/Laboratory Medicine,
‡Department of Anesthesiology,
Medical University of South Carolina,
Charleston, SC 29425

ABSTRACT

Hydroxyethyl starch is commonly used as a plasma volume expander in the surgical patient. Although it is generally considered a safe plasma substitution, some reports of an acquired von Willebrand’s disease-like syndrome have been documented. To examine this further, von Willebrand factor: ristocetin cofactor activity (RCOF) was measured in two groups of patients perioperatively, following hydroxyethyl starch infusion and at 30, 60, and 240 minutes following either deamino-8-D-arginine vasopressin (DDAVP) (group I, n = 12) or saline (group II, n = 11). Following hydroxyethyl starch infusion, ristocetin cofactor activity decreased to 58 percent (group I) and 55 percent (group II) of their respective baseline values. After infusion of DDAVP, mean ristocetin cofactor activity in group I increased significantly to 95 percent at 30 minutes and 100 percent of baseline at 60 minutes. Mean ristocetin cofactor activity levels in group II, however, remained decreased, 69 percent and 57 percent of baseline at the same time points. There was no statistical difference between groups before or immediately after hydroxyethyl starch administration or at 240 minutes post-DDAVP or saline infusion. It is our conclusion that DDAVP is a safe therapy for the mild coagulopathy infrequently associated with hydroxyethyl starch administration.

Introduction

Hydroxyethyl starch (HES), a highly branched polysaccharide with an average molecular weight of 480 Kd, is commonly used as a plasma volume expander in patients undergoing surgery. Its oncotic properties, long-half-life in circulation, essential absence of risk of infectious disease transmission, low incidence of anaphylactic reactions and low cost compared to using albumin, make it almost ideal for this purpose.1 However, there have been several reports of a bleeding diathesis secondary to an acquired von Willebrand’s disease-like syndrome developing in patients following infusion of HES.2,3,4
Desmopressin (Deamino-8-D-arginine vasopressin, DDAVP), a synthetic analogue of arginine vasopressin, is capable of stimulating release of von Willebrand factor protein from endothelial storage sites. Because of this effect, it has been used successfully as a therapy of mild and moderate hemophilia A, type I, IIa von Willebrand's disease, and in the therapy of qualitative platelet defects associated with uraemia and cirrhosis. The objective of this study was to monitor the effect of changes in von Willebrand factor: ristocetin cofactor activity associated with sequential HES and DDAVP therapy.

Materials and Methods

Following an institutional Review Board approved protocol, 23 patients undergoing surgical procedures within an expected blood loss of <750 ml were enrolled in the study after informed consent was obtained.

After induction of anesthesia, 6 percent HES was administered, 20 ml/kg, to all subjects at a rate to meet intraoperative fluid requirements and to a volume not to exceed 1500 ml. Subjects were then randomized to receive either a 10 ml solution containing 0.3 µg/kg of DDAVP (group I, n = 12) or 10 ml of normal saline (group II, n = 11).

Blood samples were drawn perioperatively, after infusion of HES and at 30, 60, and 240 minutes after study drug administration. Von Willebrand factor activity (ristocetin cofactor activity, RCoF) was measured at each of these time points by a method employing agglutination of lyophilized platelets in the presence of ristocetin. Statistical analysis of data was performed by ANOVA on repeated measurements.

Results

Perioperative von Willebrand factor: RCoF activity in group I ranged from 65 to 128.3 U/dl with a mean 90.4 U/dl compared to a range of 46.3 to 177.6 U/dl with a mean of 114.5 U/dl in group II. The group means were not statistically different.

Following hydroxyethyl starch infusion, 12 of the 23 subjects (7 in group I and 5 in group II) had von Willebrand factor: RCoF activity levels of <50 U/dl; of these, 5 (2 in group I and 3 in group II) were actually <30 U/dl, a level below which the bleeding time can be shown to be prolonged. For purposes of analysis all subsequent data points were expressed as percent of perioperative baseline values for each group at each time point measured (table I). Thus, in the DDAVP group, group mean von Willebrand factor: RCoF activity values were 57.9 ± 24.3 percent of base levels while the saline group mean was 54.6 ± 14.4 percent. These group means percents were not statistically different.

Following infusion of DDAVP in group I, values increased in 95 percent at 30 minutes and 107 percent of baseline at 60 minutes. Group II mean values, however, remained decreased, being 69 percent and 57 percent of baseline values, respectively, at each of these timepoints. These differences at 30 and 60 minutes were both statistically significant. There was no difference between groups before or immediately after HES administration or at 240 minutes post DDAVP or saline infusion.

Of interest was the finding of 2 patients in the saline group in whom the depression of von Willebrand factor: RCoF activity continued to be abnormal, i.e., <40 U/dl even at the 240 minute point post HES saline infusion. However, neither of these patients experienced excessive bleeding nor required red cell transfusion therapy.

None of the patients in group I had evidence of electrolyte imbalance associated with DDAVP use or clinical manifestations of a hypercoagulable state.
TABLE I
von Willebrand: Ristocetin Cofactor Activity

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Between Group Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 12)</td>
<td>(n = 11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DDAVP</td>
<td>Saline</td>
<td></td>
</tr>
<tr>
<td>Pre-operative*</td>
<td>100.0 ± 00.0</td>
<td>100.0 ± 00.0</td>
<td>NS</td>
</tr>
<tr>
<td>After hydroxyethyl starch</td>
<td>57.9 ± 24.3</td>
<td>54.6 ± 14.4</td>
<td>NS</td>
</tr>
<tr>
<td>After study drug</td>
<td>95.6 ± 32.7</td>
<td>69.1 ± 33.1</td>
<td>0.05</td>
</tr>
<tr>
<td>1 Hour after study drug</td>
<td>107.3 ± 39.7</td>
<td>56.8 ± 21.4</td>
<td>0.01</td>
</tr>
<tr>
<td>4 Hours after study drug</td>
<td>91.3 ± 39.6</td>
<td>74.4 ± 32.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Group mean ristocetin cofactor activity levels are expressed as a percentage of preoperative group means.

Discussion
Our study confirms that hydroxyethyl starch causes a reduction from baseline levels in von Willebrand factor: Ristocetin cofactor activity in essentially all patients receiving this volume expander. This effect as demonstrated by several studies appears to be primarily dilutional rather than directed at the von Willebrand component of the factor VIII complex. Strauss was able to demonstrate in a series of in vitro studies that hydroxyethyl starch had minimal effect on coagulation assays and that its effect in vivo on coagulation was in a dose-related fashion.

Of interest in our study was the finding that markedly diminished von Willebrand factor: RCoF activity (<35 U/dl) in the control group persisted for 90 minutes in 3 of 11 patients and for 120 minutes in 2 of these individuals. Baseline values in none of these patients suggested an underlying von Willebrand’s disease nor did any individual have a history of a bleeding diathesis. In contrast, in the DDAVP infusion group, a 1.5 to approximately 4 fold increase in von Willebrand factor: RCoF activity from the HES—induced nadir was readily demonstrated. The exact mechanism of DDAVP action is unknown; however, it appears to induce von Willebrand factor release from Weibel-Palade body storage sites in endothelial cells.

Since tissue plasminogen activator levels also rise with DDAVP use, its effect appears to be a generalized stimulation of endothelial cells. A recent study by Sloand and coauthors suggest DDAVP may have an additional ameliorating effect on the coagulation process by stimulating redistribution of cytoplastic platelet glycoprotein Ib to the platelet surface. This glycoprotein is the platelet receptor for factor VIII von Willebrand factor; thus, the net effect of this drug would be to ensure enhanced platelet function. There was no evidence of hypercoagulability nor hynema-tremia associated with DDAVP use in our study group.

In summary, hydroxyethyl starch administration does cause a predictable decrease in von Willebrand factor: ristocetin cofactor activity. A statistically significant increase in RCoF activity was produced by DDAVP following hydroxyethyl starch use which persisted for at least 240 minutes post infusion. It appears that DDAVP is a safe treatment with a mild coagulopathy infrequently associated with hydroxyethyl starch administration.
References


