Comparison of coagulation factors and blood loss between O and non-O blood types following hydroxyethyl starch infusion

Soo Joo Choi, Hyun Joo Ahn, and Jae Ik Lee

Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Individuals with type O blood are more likely to have reduced factor VIII and von Willebrand factor levels compared to their non-O counterparts. Hydroxyethyl starch (HES), which is widely used for blood volume replacement, can induce coagulopathy. Therefore, we tested whether blood type O patients show more coagulopathy and blood loss than non-O patients after infusion of 6% HES.

Methods: Thirty-four non-O and 20 type O patients scheduled for posterior lumbar interbody fusion (PLIF) involving 3 vertebrae or less from June 2007 to August 2008 were enrolled. Fifteen ml/kg of 6% HES was administered during the operation. Coagulation profiles was checked at pre-infusion (T0), 5 min after the end of infusion (T1), 3 hr after the end of infusion (T2), and 24 hr after the end of infusion (T3). Bleeding was measured during and after surgery for 24 hours.

Results: Baseline factor VIII concentration was lower and aPTT was longer in type O patients compared to those of non-O patients. 6% HES infusion decreased most of the coagulation factors at T1 in both groups, which were recovered in a time dependent manner. Factor VIII and aPTT of blood type O patients fell off the normal range at T1. However, other coagulation factors, thromboelastography variables, and blood loss were not different between the groups.

Conclusions: Despite inborn low factor VIII which further decreased shortly after HES infusion, blood type O patients did not show more blood loss than non-O blood type after 15 ml/kg of HES infusion in PLIF surgery. (Korean J Anesthesiol 2010; 58: 344-350)

Key Words: Blood loss, Blood type, Coagulation, Factor VIII, Hydroxyethyl starch, Thromboelastography.
Introduction

Posterior lumbar interbody fusion (PLIF) is usually conducted in elderly patients and continuous bone bleeding and oozing throughout the operation is a frequent finding. Instead of rapid infusion of large amount of crystalloid solutions which can be a burden to elderly patients with limited cardiovascular reserve, hydroxyethyl starch (HES) is commonly used to replace intravascular volume for PLIF.

Hydroxyethyl starch (HES), a synthetic colloid, readily allows a 1 : 1 replacement and remains longer in the intravascular space compared with crystalloid solutions [1]. However, HES can induce coagulopathy due to inhibition of endothelial cell activation [2], reduced release of factor VIII/von Willebrand factor (VWF) [3], and impairment of platelet function and fibrin polymerization [4,5]. Individuals with type O blood are reported to have an increased risk of spontaneous skin and mucous membrane hemorrhage [6] and lower amounts of circulating factor VIII/VWF than patients with other blood types [7-10]. Therefore, the possibility of coagulopathy and aggravated bone bleeding and oozing in O blood type patients by HES infusion could have an important implication in PLIF.

In the present research, we studied the difference in coagulation and bleeding between the O and non-O blood types after infusion of 15 ml/kg of 6% HES to patients undergoing posterior lumbar interbody fusion (PLIF) involving 3 vertebrae or less. We hypothesized that blood type O patients would show more coagulopathy and blood loss after HES infusion than non-O blood types in PLIF.

In addition, we followed the coagulation profile for 24 h after HES infusion to determine how long its effects are sustained.

Materials and Methods

This prospective study was approved by the Institute of Research Board of our hospital and written informed consent was obtained from all patients. All cases of PLIF of three vertebrae or less from June 2007 to August 2008 were subjected to the study. Exclusion criteria were patient’s refusal, American Society of Anesthesiologist Physical Status (ASA) 3 or 4, previous back surgery, the presence of cardiovascular disease, cerebral vascular disease, hepatic, pulmonary, or renal disease, hemoglobin <12 g/dl, platelet count <150 × 10^3/μl, coagulopathy, taking medications likely to alter coagulation less than 2 weeks before the study. Finally, 34 non-O and 20 O blood type patients were enrolled.

No patient received premedication. Intraoperative monitoring included a three lead electrocardiogram, non-invasive and invasive arterial pressures, pulse oximetry, expired CO_2, oropharyngeal temperature, and urine output. Tracheas were intubated after administering thiopental sodium (3 to 5 mg/kg) and rocuronium (0.6 mg/kg). An arterial line, a 16 G peripheral line, and a Foley catheter were catheterized and secured after anesthesia induction. Anesthesia was maintained with inhaled sevoflurane (1.0 – 2.5 vol%) in a mixture of oxygen and air (50% : 50%) and continuous infusion of remifentanil (0.02 – 0.25 μg/ kg/min) to maintain blood pressure and heart rate within 20% of baseline values.

Fifteen ml/kg of 37°C Voluven (Voluven®, Fresenius Kabi, Germany) was infused via the 16G peripheral line at a rate of 10 ml/kg/hr using blood warmer (Flotem, Hankook Vaccine inc., Korea) from the start of subperiosteal dissection. Crystalloid was administered at a rate of 10 ml/kg/h.

Blood sampling was performed for coagulation profile and hematocrit before colloid infusion (T0), 5 minutes after the end of infusion (T1), 3 hours after the end of infusion (T2), and 24 hours after the end of infusion (T3). Thromboelastography (TEG) was checked at T0, T1 and T2. Blood samples were drawn using arterial lines after removing 10 ml of blood to prevent heparin contamination. Blood was collected into Vacutainer tubes (Vacutainer™, Becton Dickinson, USA) containing 0.129 mol/L of trisodium citrate for coagulation tests. Factor VIII activity was measured using an automated coagulation analyzer (STA-R evolution®, Diagnostica Stago, France) with aPTT reagent (C.K Prest, Diagnostica Stago, France) and factor VIII-deficient plasma (Diagnostica Stago, France). An Enzyme-Linked Immunofluorescence Assay was used for VWF : Ag on a VIDAS (BioMerieux, France) with VWF : Ag™ reagent (BioMerieux, France). TEG® tracings were obtained from whole blood on a Thrombelastograph 3.000 C™ (Haemoscope Corp, USA). TEG provides global information on the entire coagulation process and measures the viscoelastic properties of blood in vitro [11]. In the components of TEG, reaction time (r) means initial fibrin formation, coagulation time (k) means fibrin formation velocity, the alpha angle indicates the rapidity of fibrin buildup, maximal amplitude (MA) indicates the strength of the fibrin clot. The coagulation index (CI) represents the overall coagulation status, and is calculated as CI = −0.1227r + 0.0092k + 0.1655MA − 0.0241 alpha angle − 7.7922 [12].

Bleeding was measured during and after surgery for 24 hours; Intraoperative estimated blood loss = (volume in the suction bottle − amount of irrigation fluid) + amount of blood on the surgical field and drape + amount of blood on surgical pads [fully soaked: 20 ml, half soaked: 10 ml]. Postoperative blood loss = amount of blood drainage in the postanesthesia care unit and ward.

Patients were transfused if their hematocrit fell to 24%. Fresh frozen plasma transfusion was indicated when the International Normalized Ratio (INR) was >2.0 or cryoprecipitate when fibrinogen levels were <100 mg/dl.
Statistical analysis

The primary outcome variable was the difference in the amount of blood loss during and for 24 hours of operation between the non-O and O groups. The expected differences in means were set at 300 ml with an expected standard deviation of 300 ml. A sample size of 17 in each group was required to achieve a power of 80% with an alpha error of 0.05. Student’s t-test or the Mann-Whitney Test was used depending on the normality of the data. For comparisons before and after colloid infusion, we used one-way repeated measures analysis of variance with Holm-Sidak post hoc tests. All P values were two tailed, and a P value < 0.05 was considered significant.

Results

No patients were excluded due to protocol violation and none received fresh frozen plasma or cryoprecipitate during the study period.

There was no difference in demographic and operative profiles between the non-O and O groups. The amount of crystalloid and HES administered during operation was similar between the two groups (Table 1).

Factor VIII was lower in the O group compared to the non-O group before HES infusion and throughout the study period (P < 0.05) (Fig. 1). The time dependent changes of factor VIII after HES infusion were similar for both groups. Factor VIII decreased at T1 in both groups, which made factor VIII fall off the normal range in the O group. However, factor VIII was increased more than the value of T0 at T2 and T3 in both groups (Table 2). The magnitude of decrease of factor VIII at T1 was not different between the groups (decreased proportion of factor VIII at T1: non-O group 19.6 ± 21.3% vs. O group 24.9 ± 27.1%, P > 0.05) and correlated with the magnitude of decrease of

Table 1. Demographic Data

|                     | Non-O (n = 34) | O (n = 20) |
|---------------------|---------------|------------|
| Sex (M/F)           | 11/23         | 11/9       |
| ASA (1/2)           | 11/23         | 11/9       |
| Age (yr)            | 58.7 ± 10.5   | 58.5 ± 10.1|
| Weight (kg)         | 66.2 ± 10.9   | 66.3 ± 9.7 |
| Height (cm)         | 160.4 ± 7.8   | 161.0 ± 10.2|
| OP                  |               |            |
| Vertebræ (1/2/3)    | 13/19/2       | 8/10/2     |
| Mean                | 1.7 ± 0.6     | 1.7 ± 0.7  |
| Duration of operation (min) | 228 ± 61 | 223 ± 82  |
| Crystalloid (ml)    | 2,344 ± 850   | 2,493 ± 1,417|
| HES (ml)            | 962 ± 145     | 964 ± 145  |

Values are mean ± SD. There were no differences between the non-O and O groups. OP: posterior lumbar interbody fusion. Vertebræ: number of operated vertebrae. Mean: mean number of operated vertebrae. HES: hydroxyethyl starch.

Table 2. Coagulation

|                | Non-O | O  |
|----------------|-------|----|
| Hematocrit (%) |       |    |
| Normal range   |       |    |
| T0             | 31.8 ± 43.8 | 30.7 ± 4.1 |
| T1             | 29.8 ± 4.5  | 28.9 ± 5.0  |
| T2             | 28.7 ± 4.3  | 28.7 ± 4.3  |
| T3             |           |    |
| T0             | 37.5 ± 2.8  | 30.0 ± 5.1  |
| T1             | 150 ± 40    | 135 ± 46    |
| T2             | 124 ± 28    | 119 ± 34    |
| T3             | 132 ± 28    | 126 (45)    |
| PLT (x10^3/µl) |       |    |
| Normal range   |       |    |
| T0             | 141 ± 316  | 153 ± 33   |
| T1             | 124 ± 24   | 127 ± 33   |
| T2             | 124 ± 28   | 124 ± 28   |
| T3             |           |    |
| T0             | 150 ± 40†  | 135 ± 46†  |
| T1             | 124 ± 28   | 119 ± 34†  |
| T2             | 119 ± 34†  | 126 ± 28†  |
| T3             |           |    |
| PT (INR)       |       |    |
| Normal range   |       |    |
| T0             | 0.9 ± 1.1  | 1.3 ± 1.7  |
| T1             | 1.2 ± 0.1  | 1.2 ± 0.1  |
| T2             | 1.2 ± 0.1  | 1.2 ± 0.1  |
| T3             |           |    |
| T0             | 1.1 ± 0.1  | 1.1 ± 0.1  |
| T1             | 1.2 ± 0.1  | 1.2 ± 0.1  |
| T2             | 1.2 ± 0.1  | 1.2 ± 0.1  |
| T3             |           |    |
| aPTT (sec)     |       |    |
| Normal range   |       |    |
| T0             | 32.0 ± 41.2| 34.6 ± 2.8 |
| T1             | 38.9 ± 3.9†| 34.7 ± 4.4 |
| T2             | 37.7 ± 4.0†| 37.7 ± 4.0†|
| T3             |           |    |
| T0             | 36.6 ± 2.8†| 41.1 ± 4.2†|
| T1             | 32.6 ± 5.3†| 38.2 ± 5.4†|
| T2             | 263 ± 68†  | 40.2 (4.8)†|
| T3             |           |    |
| Fibrinogen (mg/dl) |       |    |
| Normal range   |       |    |
| T0             | 182 ± 380  | 253 ± 56† |
| T1             | 183 ± 27   | 269 ± 53† |
| T2             | 177 ± 30   | 263 ± 68† |
| T3             |           |    |
| T0             | 263 ± 68†  | 32.6 ± 5.3†|
| T1             | 263 ± 68†  | 38.2 ± 5.4†|
| T2             | 182 ± 33†  | 40.2 (4.8)†|
| T3             | 171 ± 33   | 270 (77)† |
| VWF: ag (%)    |       |    |
| Normal range   |       |    |
| T0             | 50 ± 150  | 119 ± 52 |
| T1             | 112 ± 57  | 124 ± 53 |
| T2             | 141 ± 55  | 133 ± 49 |
| T3             |           |    |
| T0             | 111 ± 48  | 102 ± 42 |
| T1             | 102 ± 42  | 133 ± 49 |
| T2             | 124 ± 53  | 136 (67)†|
| T3             |           |    |
| Factor VIII (%)|       |    |
| Normal range   |       |    |
| T0             | 60 ± 150  | 111 ± 30 |
| T1             | 86 ± 38‡  | 153 ± 57†|
| T2             | 150 ± 47† | 150 ± 47†|
| T3             |           |    |
| T0             | 78 ± 25‡  | 58 ± 26† |
| T1             | 78 ± 25‡  | 58 ± 26† |
| T2             | 105 ± 72† | 113 (47)‡|
| T3             |           |    |

Values are mean ± SD. T0: pre-infusion, T1: 5 min after the end of infusion, T2: 3 hr after the end of infusion, T3: 24 hr after the end of infusion. PLT: platelet. Between the groups: *P < 0.05 compared to the counterpart of the non-O group. Within the group: †P < 0.05 compared to the T1, T2, T3. ‡P < 0.05 compared to T0, T2. ††P < 0.05 compared to T1, T2. §P < 0.05 compared to T0, T1, T2. **P < 0.05 compared to T1, ***P < 0.05 compared to the T0, ††P < 0.05 compared to the T0, T1.
hematocrit (decreased proportion of hematocrit at T1; non-O group 18.6 ± 10.4% vs. O group 20.1 ± 10.6%, P > 0.05) (Fig. 2). aPTT was prolonged in the O group compared to the non-O group before HES infusion and throughout the study period (P < 0.05) (Fig. 3).

Other coagulation profiles did not differ between the two groups. For the time dependent changes, platelet and fibrinogen decreased at T1. Fibrinogen restored at T3, but platelets did not restore during the first 24 h in both groups. PT and VWF remained stable during the study period (Table 2).

There were no differences in the TEG results between the groups. For the time dependent changes of TEG variables, reaction time (r) and coagulation time (k) were shortened and the alpha angle and coagulation index (CI) increased at T2 in both groups (Table 3).

The total amount of blood loss and transfusion was not different between the two groups (Table 4).

**Discussion**

Blood type O patients showed decreased factor VIII and increased aPTT compared to the non-O patients from T0, and transient further deterioration shortly after HES infusion made factor VIII and aPTT off the normal range in blood type O group. There were no differences between the non-O and O groups. Number: number of patients. Intraop: intraoperative, Postop: from the end of operation to the postoperative 24 hours.

| Table 4. Blood Loss |
|---------------------|
| **Non-O** (n = 34)  | **O** (n = 20) |
| **Blood loss (ml)** |                  |
| Total               | 1,379 ± 593      | 1,677 ± 961      |
| Intraop             | 1,241 ± 578      | 1,561 ± 934      |
| Postop              | 137 ± 96         | 116 ± 95         |
| **Red blood cell transfusion (ml)** |                  |
| Total               | Number | 11 | 7 |
| Amount              | 843 ± 358 | 1,143 ± 736 |
| Intraop             | Number | 3 | 5 |
| Amount              | 533 ± 185 | 1,152 ± 834 |
| Postop              | Number | 10 | 3 |
| Amount              | 768 ± 270 | 747 ± 185 |

Values are mean SD. There were no differences between the non-O and O groups. Number: number of patients. Intraop: intraoperative, Postop: from the end of operation to the postoperative 24 hours.

**Table 3. Thromboelastography**

|                  | **Non-O** |                  | **O** |
|------------------|-----------|------------------|
|                  | **T0**    | **T1**           | **T2** |
|                  | **T0**    | **T1**           | **T2** |
|                  | R (min)   | 13.8 ± 5.5       | 11.7 ± 5.5       | 8.4 ± 2.3 *       |
|                  | K (min)   | 6.7 ± 2.9        | 5.7 ± 2.6        | 4.6 ± 2.8 *       |
|                  | Ma (min)  | 49.4 ± 4.7       | 45.8 ± 7.5 †     | 47.7 ± 6.7       |
|                  | Angle (deg) | 35.6 ± 9.0     | 38.7 ± 11.5      | 47.3 ± 9.9 *      |
|                  | Ly30 (%)  | 3.8 ± 5.6        | 5.0 ± 11.3       | 7.8 ± 11.8       |
|                  | Ly60 (%)  | 9.6 ± 9.9        | 10.4 ± 15.0      | 14.7 ± 18.0      |
|                  | Index     | −1.0 ± 1.5       | −1.1 ± 1.7       | −0.3 ± 1.2 *      |

Values are mean ± SD. There were no differences between the non-O and O groups. T0: pre-infusion, T1: 5 min after infusion, T2: 3 hr after infusion. Within the groups: *P < 0.05 compared to T0 and T1. † P < 0.05 compared to T0.
O patients. However, most coagulation factors were rapidly recovered and blood loss and the amount of transfusion were not different between the two groups.

The underlying mechanisms of decreased factor VIII in the blood type O are not clear. Each blood group has specific antigens (A, B, and H determinants) and the only circulating plasma glycoproteins expressing N-linked ABH antigens are factor VIII/VWF and α₂-macroglobulin [13,14]. O’Donell et al.[8] suggested that increased clearance is the underlying mechanism for low factor VIII levels in the O blood group because factor VIII that expresses H antigen is removed from circulation more rapidly via distinct hepatic receptors that metabolize the terminal fucose of H antigen.

HES can induce coagulopathy due to inhibition of endothelial cell activation [2], reduced release of factor VIII/VWF [3], and impairment of platelet function and fibrin polymerization [4,5]. The inhibitory mechanisms involve forming a mechanical barrier over the cell surface or binding to coagulation factors by colloid macromolecules [2,15-17].

According to our results, factor VIII was lower in the blood type O patients from the start, and HES infusion transiently further decreased factor VIII which fell below the normal range in the O group. aPTT assesses the function of all coagulation factors, except factor VII and XIII, and is a good indicator of factor VIII. However, the proportional change of factor VIII and the approximate degree of hemodilution after HES infusion were similar regardless of blood type (Fig. 2). From this result, we assumed that the decrease of factor VIII by 15 ml/kg of HES is mainly due to hemodilution and not related to the inhibition of factor VIII out of proportion by O blood type.

There have been few studies dealing coagulopathy after HES infusion according to the blood types [10,18]. One study examined the hemostatic effect of 6% HES in patients undergoing abdominal surgery [18]. HES was infused according to blood loss, hemodynamic variables and duration of surgery up to 30 ml/kg and the mean speed of administration was 10 ml/kg/h like ours. Most of the results were in line with our study, however, the decreases of factor VIII and VWF after HES infusion were more pronounced than the decrease of the hematocrit. The amount of HES and methods of administration seem to have affected the results. Factor VIII, VWF, and variables of TEG stayed within the normal ranges in this study [18]. The other study conducted acute normovolemic hemodilution (ANH) with HES in patients undergoing various levels of spine surgery [10]. In this case, the proportional decrease of factor VIII and VWF 30 minutes after ANH was also beyond that expected from hemodilution alone and they fell below the normal range in the O group. Considering all these results, speed and amount both seem to be important to determine the effect of HES infusion on coagulation factors with possibly more weight on the speed. Fifteen ml/kg of HES infused at a rate of 10 ml/kg/h did not produce significant coagulation abnormality in the O blood types in our study.

In the current study, we searched a 24 hour-effect of HES infusion. Infusion of 15 ml/kg of HES decreased platelet, fibrinogen, and factor VIII at T1. Platelet remained decreased throughout the study period. Fibrinogen remained decreased until T2 and restored to preinfusion level at T3. Factor VIII rebounded more than T0 level at T2 and T3. The net hemostatic effect of these changes in coagulation factors is hard to grasp. In the view point of TEG which assesses overall hemostasis, coagulation was maintained at T1 and enhanced at T2 in both groups without between-group differences (Table 3). Hemodilution decreases antithrombin III more than thrombin and facilitates coagulation [19-21], and hemodilution induced hypercoagulation is represented by a shortened r and k in TEG [22,23]. Therefore, enhancement of coagulation by hemodilution with HES might have counteracted the decrease of coagulation factors at T1. Increased coagulation at T2 in TEG in both groups seems to be related to surgical stress induced hypercoagulation [24].

The amount of blood loss was not different between the O and non-O blood types in the current study. Previous two studies also reported no difference in blood loss [10,18]. The reason might be that hemodilution counteracted transient decrease of coagulation factors after HES infusion. Secondly, most coagulation factors can be easily synthesized from liver and can be rapidly released from endothelium and platelets to replace losses [25-27]. Thirdly, only 30 – 50% of factor VIII is known to be required for adequate hemostasis during surgery [26,28]. Low factor VIII alone, therefore, would unlikely cause difference in blood loss in the O blood type. In our study, other coagulation factors and TEG variables were not different between the two groups.

Besides these factors, there are other factors that determine coagulation status and bleeding. During surgery, there are major disturbances in coagulation and inflammatory systems because of hemorrhage/hemodilution, blood transfusion, tissue injury, and surgical stresses. In the presence of massive hemorrhage and severe hemodilution, the initiation of thrombin generation is delayed by reduced Factor VII, and the propagation is reduced by the gross reduction of procoagulant serine protease zymogens and accelerators. Allogeneic blood transfusions increase thrombin generation and hemostasis. Surgical patients have varied degrees of vascular injury. Acute inflammatory responses associated with vascular injury often result in elevated cytokines, platelet count, fibrinogen, and VWF-Factor VIII levels over the normal limit. Tissue injury promotes procoagulant activity and inflammation [29]. All these factors might have influenced final coagulation status and
blood loss.

In the current study, we used 15 ml/kg of Voluven (Voluven®, Fresenius Kabi, Germany) and showed no detrimental effect of HES on blood loss in the O blood type. However, higher volumes or different types of HES might bring different results [30]. Therefore, further studies are needed to confirm the maximum volume that can be safely administered or the effect of different types of HES in O blood type patients.

In conclusion, blood type O patients showed decreased factor VIII and increased aPTT compared to the non-O patients from the beginning, and transient further deterioration shortly after 15 ml/kg of Voluven infusion. However, other coagulation factors and TEG variables were not different, neither the amount of blood loss between the two groups. Therefore, 15 ml/kg of Voluven does not further increase the risk of bleeding in the blood type O patients and can be safely administered during PLIF.

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