The Hemostatic Profiles of Patients with Type O and Non-O Blood After Acute Normovolemic Hemodilution with 6% Hydroxyethyl Starch (130/0.4)

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BACKGROUND: Individuals with Type O blood have been reported to have a tendency toward reduced Factor VIII and von Willebrand Factor (vWF) levels. If this is true, patients with Type O blood might be vulnerable to coagulopathy during acute normovolemic hemodilution using hydroxyethyl starch (HES), both from hemodilution as well as HES-related coagulopathy.

METHODS: Thirty non-O and 15 type O ASA 1 or 2 patients scheduled for spinal surgery involving more than two spinal levels were enrolled for the study. After anesthesia induction, 30% of the estimated blood volume was removed, and the volume was simultaneously replaced with 6% HES (130/0.4). Coagulation profiles were measured before (T_0) and 30 min after acute normovolemic hemodilution (T_{30}).

RESULTS: Factor VIII activity, vWF antigen levels (vWF:ag), and vWF ristocetin cofactor activity (vWF:RCof) were lower in the O group than in the non-O group before and after acute normovolemic hemodilution, and decreased below the normal range in the O group after acute normovolemic hemodilution. The decrease was beyond that expected from hemodilution alone. Maximum amplitude and coagulation index of the thromboelastogram decreased below the normal range in the O group after acute normovolemic hemodilution. The decrease in vWF:ag was related to the degree of blood loss, and was greater in patients in the O group.

CONCLUSIONS: Patients with Type O blood may have increased coagulation compromise, and greater dilution of Factor VIII activity, vWF:ag, and vWF:RCof after acute normovolemic hemodilution with HES.

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Acute normovolemic hemodilution (ANH) is a method of blood sparing during surgery. To be effective, ANH typically involves removal of more than 30% of the patient's blood volume, concurrently restoring the circulating blood volume using an acellular fluid shortly before surgical blood loss (1–3).

Hydroxyethyl starch (HES) is commonly used during ANH as an intravascular volume replacement solution, because it readily allows a 1:1 replacement and remains in the vascular space. However, HES, especially if administered in large volumes, can induce coagulopathy because of reduced release of factor VIII/von Willebrand Factor (vWF), impaired platelet function, and hemodilution (4–11). Recently developed 6% HES (130/0.4) solutions can also impair coagulation, but to a lesser degree, because of low molecular weight and degree of substitution (6,10).

Several studies have reported that individuals with Type O blood are at increased risk of spontaneous skin and mucous membrane hemorrhage (12) and have smaller amounts of circulating Factor VIII/vWF than patients with other blood types (13–15). If true, patients with Type O blood could develop coagulopathy after ANH, even with 6% HES (130/0.4), which causes less coagulopathy.

We undertook this study to evaluate the effect of ANH using 6% HES (130/0.4) on coagulation profiles in patients with Type O blood and non-O blood. We hypothesized that patients with Type O blood have lower Factor VIII/vWF levels, and that this can be aggravated after ANH, resulting in increased blood loss compared with that in patients with other blood types.

METHODS

After approval from our hospital ethics committee, between October 1, 2004 to June 30, 2005, 30 patients with Type non-O blood and 15 patients with Type O blood, who provided written informed consent, were enrolled in this study. Patients were ASA 1 or 2, and

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were scheduled for posterior laminectomy and internal fixation at more than two spinal levels. Exclusion criteria were the presence of cardiovascular diseases, cerebral vascular disease, hepatic, pulmonary, or renal disease, hemoglobin <12 g/dL, platelet count $<150 \times 10^3/\mu L$, coagulopathy, taking medication that likely alters coagulation <2 wk before the study, or an allergic reaction to HES.

The attending anesthesiologist was unaware of the patient's blood type. All operations were performed by the same surgeon.

No patient received premedication. Intraoperative monitoring included a three-lead electrocardiogram, blood pressure cuff, oxygen saturation, expired CO_2, oral temperature, arterial and central venous pressure, and urine output. Tracheas were intubated after administering thiopental sodium (3–5 mg/kg) and rocuronium (0.6 mg/kg). An arterial line, a central line, another 16G peripheral line, and a Foley catheter were secured after anesthesia induction. Anesthesia was maintained with inhaled sevoflurane in a mixture of oxygen and N_2O (50:50). After prone positioning, 30% of the total estimated blood volume (male 70 mL/kg, female 65 mL/kg) was withdrawn into 450 mL hemodilution bags (CDPA-1 anticoagulant bag) from the arterial line, and the same amount of 37°C-heated 6% HES (130/0.4, Voluven™, Fresenius Kabi, Germany) was infused via the 16G peripheral line, while monitoring central venous and cuff blood pressures.

During ANH, ephedrine was administered for a mean arterial blood pressure (MBP) <65 mm Hg. Dopamine infusion was started in cases of persistent hypotension despite ephedrine administration. The incidence of hypotension and the amount of drugs administered during ANH were recorded. ANH and all measurements were completed before the operation started.

Blood samples were drawn using arterial lines after removing sufficient 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. Vacutainer tubes containing EDTA were used for hematocrit and platelet count determinations. A syringe containing 0.33 mL of blood was immediately transferred to produce thromboelastogram (TEG®) tracings. All blood sampling was done before and 30 min after ANH. Hematocrit was measured 24 h after ANH.

ABO blood groups were identified using standard agglutination assays. Hematocrit and platelet counts were performed on an H1 analyzer (Bayer Technicon, Puteaux, France). Activated partial thromboplastin time (aPTT) was measured using an automated APTT (Organon Teknika Corporation, Durham, NC). 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). vWF:ag represents the vWF antigen levels. vWF ristocetin cofactor activity (vWF:RCof) is a measure of vWF functional activity, reflecting the interaction between vWF and glycoprotein Ib. An enzyme-linked immunofluorescence assay was used for vWF:ag on a VIDAS (bioMerieux, France) with vWF-Ag® reagent (BioMerieux, France). vWF:RCof was measured using a Ristocetin Cofactor Assay kit® (Helena laboratories, USA), on a PACKS-4 (Helena Laboratories, USA). TEG tracings were obtained from whole blood on a Thrombelastograph 3.000 C™ (Hemoscope, USA).

Arterial blood gas analysis was performed at 30-min intervals during the procedure. Patients received a transfusion of red blood cells for a hematocrit of 25%, unstable vital signs (MBP <60 mm Hg, heart rate >100 bpm), or urine output of $<0.4\ mL \cdot kg^{-1} \cdot h^{-1}$ despite adequate fluid administration. Initially, the withdrawn blood was transfused in the reverse order of blood collection so that the blood transfused at the conclusion of surgery had the highest levels of erythrocytes, platelets, and coagulation factors. If the hematocrit level remained below 25% after autologous transfusion, heterologous blood was transfused with a target hematocrit of 25%. All procured blood was kept at room temperature (25°C) and transfused within 8 h of collection. Fresh frozen plasma (FFP) transfusion was indicated when International Normalized Ratio (INR) was >2.0 or fibrinogen levels were <100 mg/dL. Bleeding was measured during and after surgery for 24 h (aspiration volume, surgical fields, pad weights, suction bottles, and Hemovac).

The primary outcome variable was the difference in vWF:ag between the non-O and O group after ANH. The expected differences in means were set at 30% with an expected standard deviation of 27% after consulting Huraux et al. (16). A sample size of 14 in each group was required to achieve a power of 80% with an α error of 0.05. For coagulation profiles and TEG values between the non-O and O groups, the Student's *t*-test or the Mann–Whitney ranked sum test was used depending on the normality of data. For comparisons before and after ANH, the paired *t*-test or the Wilcoxon signed rank test was used. All *P* values were two tailed, and a $P < 0.05$ was considered significant.

RESULTS

One patient in each group was excluded from the data analysis because of a protocol violation. Therefore, 29 patients in the non-O group and 14 in the O group were assessed. Demographic and hemodilutional characteristics were similar in the two groups (Table 1).

Hematocrit, platelet, and fibrinogen levels decreased and prothrombin time/aPTT increased after ANH in both groups. The only difference in coagulation tests was aPTT, which was relatively prolonged in the O group after ANH (Table 2). No patients developed INR >2. One patient in each group developed hypofibrinogenemia (<100 mg/dl) during the operation and received 2 U of FFP.

Table 1. Demographic Profiles and Hemodilution-Related Data

	Non-O ($N = 29$)	O ($N = 14$)
Age (yr)	50.0 ± 11.7	52.3 ± 10.8
Height (cm)	157.0 ± 8.3	160.6 ± 1.0
Weight (kg)	56.0 ± 9.8	56.0 ± 13.2
Gender, M/F	9/20	4/10
Number of operated vertebra		
2–3	12 (41)	8 (57)
4–5	7 (24)	3 (21)
6–7	5 (17)	1 (7)
>8	5 (17)	2 (14)
Blood type, A/B/AB/O	15/11/3/14	
Estimated blood volume (ml)	3732 ± 679	3781 ± 955
Blood deposit volume (ml)	1012 ± 272	1150 ± 203
Replaced HES volume (ml)	960 ± 240	1086 ± 208
Duration of ANH (min)	43.8 ± 16.7	52.1 ± 21.3
Allogenic transfusion (ml)	590 ± 418	702 ± 925
Hct before ANH (%)	37.4 ± 3.3	38.5 ± 5.0
Hct after ANH (%)	25.3 ± 2.7	25.6 ± 3.5
UO (ml/h)	237 ± 123	253 ± 237
Blood loss during OP (ml)	1295 ± 686	1354 ± 752
Blood loss for 24 h (ml)	267 ± 100	301 ± 156
Hct at POD1 (%)	28.2 ± 3.9	30.6 ± 6.5

Values are given as means ± SD; values within parentheses indicate percentages.

HES = hydroxyethyl starch, ANH = acute normovolemic hemodilution, Hct = hematocrit, UO = urine output, OP = operation, POD = postoperative day.

Factor VIII activity, vWF:ag, and vWF:RCof decreased after ANH in both groups. Factor VIII activity, vWF:ag, and vWF:RCof were lower in the O group than in the non-O group before and after ANH, and decreased below the normal range after ANH in the O group (Table 2, Fig. 1). The magnitude of decrease in Factor VIII activity, vWF:ag and vWF:RCof between post-ANH and pre-ANH was not different between the two groups.

In the non-O group, maximum amplitude (MA) and coagulation index (CI) decreased after ANH but remained in the normal range. In the O group, reaction time (*R*), MA, 30 min lysis (LY30), and CI were changed after ANH, and *R*, MA, and CI decreased below the normal range in the O group. However, TEG results were not statistically different between the two groups except LY30 and 60 min lysis (LY60). LY30 and LY60 values were higher in the O group before and after ANH (Table 2). However, the magnitude of alteration of *R*, MA, and CI between post-ANH and pre-ANH was larger in the O group than the non-O group (R: −0.6 vs 7.3, MA: −4.5 vs −9.9 and CI: −0.7 vs −2.4).

The decreased percentage in Factor VIII activity, vWF:ag, and vWF:RCof was more profound than the decreased percentage in hematocrit or platelet count after ANH in both groups (Table 3).

There was no difference in the total amount of blood loss between the two groups (Table 1). The use of packed blood cells was 1.8 U versus 1.6 U in the non-O and O group, respectively, with no differences between groups.

Blood loss was larger in the patients with vWF:ag <50% without blood group difference (Fig. 2) and the proportion of patients with vWF:ag <50% was larger in the O group (63% vs 21%) after ANH.

No complications related to ANH or HES occurred. Twelve patients in the non-O group and eight in the O group had a MBP of <65 mm Hg during ANH, but this difference was not significant.

DISCUSSION

This study confirmed that O and non-O blood group populations have a different coagulation status. Factor VIII/vWF values, already decreased in the O group, further decreased below the normal range after ANH using 6% HES (130/0.4), and the decrease was beyond hemodilutional level in both groups.

There has been only one comparable study that evaluated the hemostatic profiles of patients with non-O and O type blood (16). In that study, Factor VIII/vWF values were lower in the O group before and after HES infusion, similar to that in our study. The differences are that they used 6% HES (200/0.6) and 20 mL/kg of the solution was infused for a 2 h duration without active hemodilution. We administered 6% HES (130/0.4) for <1 h, and ANH was performed. Therefore, coagulopathy developed more rapidly in our study. In the previous study, factor VIII/vWF remained within the normal range, and TEG profiles did not change in either group after the infusion. Release of factor VIII/vWF from storage sites during prolonged hours of HES infusion might have partially compensated for the shortage of these coagulation factors.

The underlying mechanisms by which these coagulation factors are lower in O blood group patients are not clear. Researchers have noted that the ABO locus itself has a direct effect on factor VIII/vWF concentration (13). Orstavik et al. (17) showed that this locus primarily affects plasma vWF levels and that the plasma factor VIII concentration is only secondarily regulated by plasma vWF levels.

Each blood group has specific antigens (A, B, and H determinants, respectively), and the only circulating plasma glycoproteins expressing N-linked ABH antigens are factor VIII/vWF and α_2-macroglobulin (18,19). Theoretically, the ABO blood group may influence the three steps of vWF; the rate of vWF synthesis, secretion by endothelial cells, or the rate of plasma clearance. O'Donell et al. (14) have suggested that increased clearance is the underlying mechanism of low vWF in the O blood group. The vWF that expresses the H antigen might be removed from circulation more rapidly via the distinct hepatic receptors which have specificity on the metabolizing terminal fucose of the H antigen (14).

HES is widely used for ANH because, unlike crystalloid solutions, it is retained in the intravascular space (4). The effects of HES on coagulation are controversial. Some investigators suggest that HES

Table 2. Coagulation Profile and Thromboelastography (TEG®)

		Non-O (N = 29)		O (N = 14)	
	Normal range	Pre-acute normovolemic hemodilution	Post-acute normovolemic hemodilution	Pre-acute normovolemic hemodilution	Post-acute normovolemic hemodilution
Hct (%)	40.4–51.3	37.4 ± 3.3	25.3 ± 2.7*	38.5 ± 5.0	25.6 ± 3.5*
PLT ($\times 10^3/\mu$l)	141–316	179 ± 38	137 ± 32*	173 ± 38	133 ± 35*
PT, INR	0.9–1.1	1.0 ± 0.1	1.3 ± 0.1*	1.0 ± 0.1	1.3 ± 0.1*
aPTT (s)	32.0–41.2	38.7 ± 3.2	42.9 ± 4.0*	40.0 ± 3.0	46.2 ± 5.7*†
Factor VIII Activity (%)	60–150	124.9 ± 39.2	79.3 ± 34.6*	83.1 ± 26.3†	47.3 ± 19.3*†
vWF:Ag (%)	50–150	110.1 ± 36.7	67.2 ± 19.7*	77.8 ± 22.5†	47.2 ± 15.9*†
vWF:RCof (%)	60–140	95.9 ± 30.7	65.8 ± 28.9*	79.4 ± 22.1	43.9 ± 17.0*†
R (mm)	19–28	27.4 ± 7.9	26.9 ± 7.2	23.5 ± 6.0	30.8 ± 8.6*
K (mm)	8–13	10.9 ± 3.0	11.2 ± 3.8	9.2 ± 3.1	11.3 ± 3.1
α angle (degree)	29–43	38.9 ± 8.0	39.3 ± 9.3	40.4 ± 9.2	40.0 ± 9.9
MA (mm)	48–60	52.4 ± 6.1	48.1 ± 7.1*	55.3 ± 6.4	45.3 ± 6.5*
LY30 (%)		1.2 ± 0.7	1.5 ± 0.7	1.8 ± 0.6†	3.3 ± 2.3*†
LY60 (%)		4.0 ± 1.4	4.6 ± 1.2	4.9 ± 1.2†	6.3 ± 1.7†
CI	−2.0 ± 2.0	−0.6 ± 1.3	−1.2 ± 1.5*	0.3 ± 1.1	−2.2 ± 1.4*

All values are given as mean ± SD.

Hct = hematocrit, PLT = platelet count, PT = prothrombin time, INR= International Normalized Ratio, aPTT = activated parital thromboplastin time. MA = maximum amplitude, CI = coagulation index. vWF:Ag = vWF antigen, vWF:RCof = vWF ristocetin cofactor activity, R = reaction time, K = coagulation time, LY30 = 30 min lysis, LY60 = 60 min lysis, CI = coagulation index.

* $P < 0.05$ versus pre-acute normovolemic hemodilution. † $P < 0.05$ versus non-O counterpart.

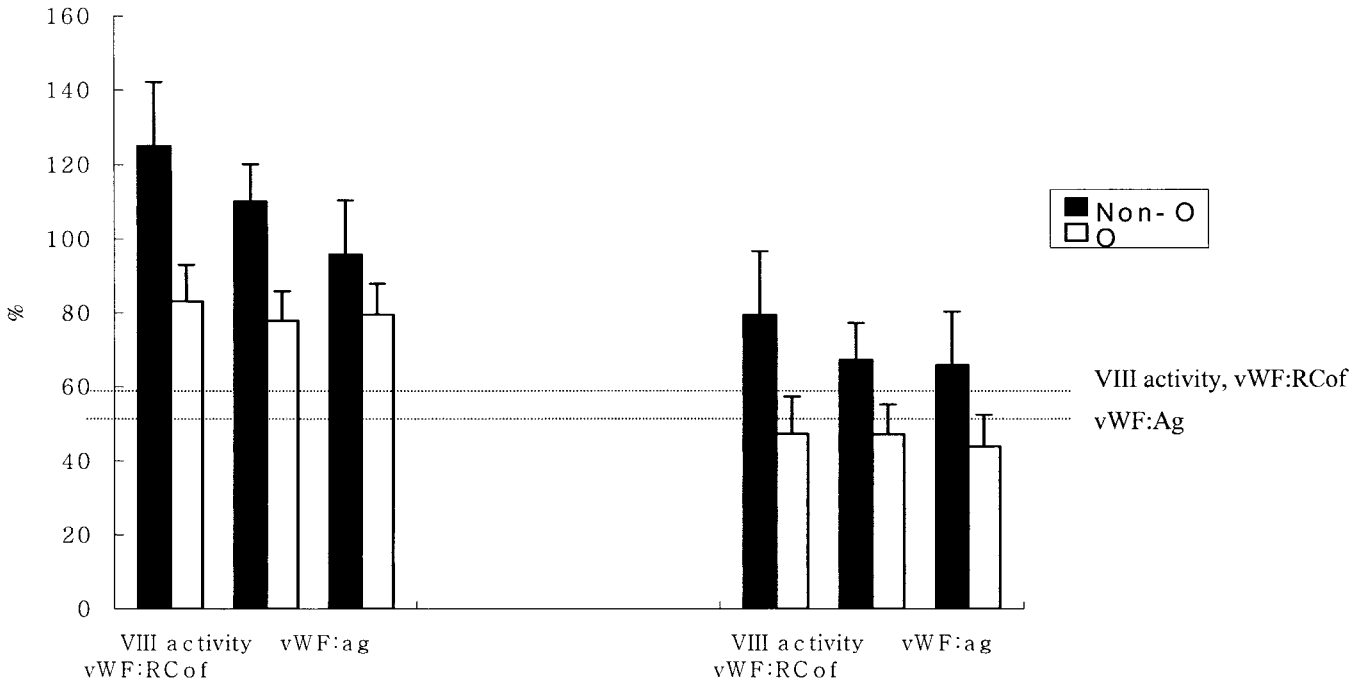

Figure 1. Factor VIII activity, vWF:ag and vWF:RCof decreased after acute normovolemic hemodilution and were lower in the O group than in the non-O before and after acute normovolemic hemodilution. vWF:ag = vWF antigen, vWF:RCof = vWF ristocetin cofactor activity, ANH = acute normovolemic hemodilution. Normal range: Factor VIII activity (60%–150%), vWF:Ag (50%–150%), vWF:RCof (60%–140%). Dotted lines indicate lower limit of normal range.

reduces factor VIII/vWF release (4–11,20–23). The possible mechanisms for this include coating endothelial cell surfaces by starch molecules, which stabilizes the endothelial cell membrane and prevents vWF release (24). This decrease in vWF subsequently results in factor VIII decrease. However, 6% HES (130/0.4), a recently introduced HES preparation with a lower molecular weight and degree of substitution, has been reported to have little or no effect on factor VIII (4,10) or TEG results (20). However, in the present study, 6% HES (130/0.4) decreased Factor VIII/vWF beyond the expected results of hemodilution, as measured by the decrease in hematocrit or platelet count (Table 3). The magnitude of decrease of Factor VIII activity and vWF:ag between post-ANH and pre-ANH was the same in both groups. Therefore, we can assume that 6% HES (130/0.4) can alter coagulation regardless of blood type.

In this study, TEG results failed to demonstrate coagulation differences between the non-O and the O

Table 3. Decreased Percentage After Acute Normovolemic Hemodilution[a]

	Non-O ($N = 14$)	O ($N = 29$)
Hct	31.9 ± 0.1	32.6 ± 0.0
PLT ($\times 10^3/\mu$l)	22.2 ± 0.1*	22.4 ± 0.1*
Fibrinogen (mg/dl)	39.1 ± 0.1*	37.7 ± 0.0*
Factor VIII activity (%)	36.4 ± 0.2*	41.5 ± 0.2*
vWF:ag	37.6 ± 0.1*	38.3 ± 0.1*
vWF:RCof	32.4 ± 0.2	44.2 ± 0.1*†

Hct = hematocrit, PLT = platelet count. vWF:Ag = vWF antigen, vWF:RCof = vWF ristocetin cofactor activity.

[a] Values are [(pre-ANH − post-ANH) × 100]/pre-ANH. All values are given as mean ± SD.

* $P < 0.05$ versus Hct. † $P < 0.05$ versus the non-O group.

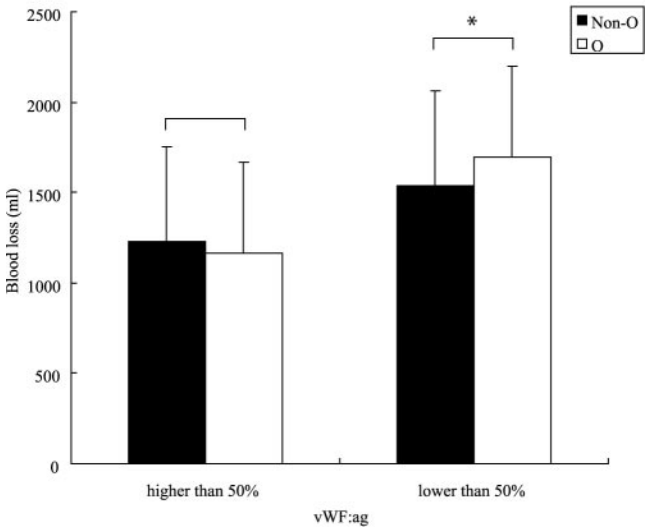

Figure 2. Blood loss was greater in the patients whose vWF:ag was lower than 50% compared with higher than 50%. *$P < 0.05$. There was no difference between the non-O and O group. vWF:ag = vWF antigen.

groups, except for LY30 and LY60 (Table 2). However, *R*, MA, and CI decreased below the normal range after ANH, and the magnitude of alteration was higher in the O group. TEG could not measure the interaction between vascular endothelium and vWF as a limitation of an *in vitro* study (25), and therefore might not be sensitive to the VIII/vWF differences between the blood groups.

The reason for higher LY30 and LY60 is not clear, but in the O group, it may be indirectly related to weak bonding inside thrombi due to lower VIII/vWF values. Prolonged *R* represents a coagulation factor deficiency, and a small MA represents final blood clot strength, which depends on platelet, coagulation factors, and fibrinogen. Low CI reflects impaired overall coagulation.

aPTT assesses the function of all coagulation factors except factor VII and XIII. It is thus a good indicator of the function of factor VIII/vWF. In our study, aPTT was more prolonged after ANH in the O group.

The only previous study comparing blood loss according to blood types underwent for abdominal surgery patients could also not prove bleeding difference (16). The abdominal surgeries ranged from herniorrhaphy to esophagectomy, and the blood loss was 0–1800 mL. Comparing blood loss among groups composed of various operations may not yield dependable data. Even though we focused on one type of surgery, in which it is expected that a large amount of blood will be shed, we included a broad spectrum of spinal surgeries, ranging from two-levels to scoliosis correction. And the non-O group included more cases of extensive surgeries (operations of more than six spinal levels: 34% vs 21%). This bias may have affected there being no difference in total blood loss (Table 1). For future study, narrowing the range of operation types might reveal a difference in total blood loss.

A previous study showed that bleeding increases when vWF:ag levels decrease below 50%, regardless of blood type (26). In the O group, the mean value of vWF:ag was about 47% after ANH, compared with 78% in the non-O group (Table 2). When we compared bleeding between the patients with vWF:ag <50% and more than 50%, the patients with vWF:ag <50% bled more (Fig. 2). The proportion of patients with vWF:ag <50% was larger in the O group (63% vs 21%). This result may imply that the absolute value of vWF:ag is the main determinant of bleeding, and that blood type O patients easily become pseudo-Type 1 vWF diseased (26).

In conclusion, this study showed that individuals with blood Type O had reduced factor VIII/vWF levels compared to patients with non-O blood. Patients with type O blood may develop changes in hemostatic factors, especially during ANH, when 6% HES (130/0.4) is used. This should be considered if patients with type O blood develop clinically significant bleeding after hemodilution with HES.

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