Blood Type O Predicts Hematoma Expansion in Patients with Intracerebral Hemorrhage

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Background: Hematoma expansion after acute spontaneous intracerebral hemorrhage (ICH) is well established to result in poor prognosis. Recent studies have demonstrated that the ABO blood type system has potential implications on hemostatic properties. The purpose of this study was to explore the potential association of blood type O with hematoma expansion in patients with ICH and validate the usefulness in predicting early hematoma expansion. *Methods:* We retrospectively enrolled consecutive patients with ICH who underwent baseline computed tomographic (CT) scan within 6 hours after onset of symptoms. The follow-up CT scan was available within 48 hours after the baseline CT scan. Hematoma expansion was defined as total volume increase more than 33% or more than 6 mL. We performed univariate and multivariate logistic regression analyses to investigate the relationship between the different types of blood (type O versus other types) and hematoma expansion. *Results:* A total of 210 patients were included in the study. Among them, 72 patients (34.3%) carried blood type O. Hematoma expansion was more common in patients with blood type O (41.7%) than those with other blood types (18.1%; $P < .001$). Furthermore, the time to baseline CT scan, blood type O, and admission Glasgow Coma Scale score were demonstrated to be independent predictors of hematoma expansion in multivariate logistic regression analysis model. The sensitivity, specificity, positive, and negative predictive values of blood type O for predicting hematoma expansion were 54.5%, 72.9%, 41.6%, and 81.9%, respectively. *Conclusions:* Our findings suggest that blood type O represents an independent predictor of hematoma expansion after ICH. Hemostasis seems to be involved in expansion and may represent an important treatment target.

Key Words: Intracerebral hemorrhage—hematoma expansion—blood type—hemostasis—predictors—stroke

Introduction

Acute spontaneous intracerebral hemorrhage (ICH) accounts for 20% of any form of stroke and contributes to high morbidity and mortality throughout the world.[1-3] Around one third of individuals with ICH are encountered with hematoma expansion, which is associated with poor outcomes and death.[4] Therefore, reduction of hematoma expansion would be beneficial for improving the prognosis following ICH.[5] Hemostasis and thrombosis systems are associated with hematoma expansion, which represent potential targets for acute ICH treatment.[6,7]

The ABO blood type system is based on the carbohydrate moieties expressed on many human cells including platelets, red blood cells, and vascular endothelium.[8] In addition, the relationship between different blood types and the risk of bleeding was observed in several diseases, such as

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obstetrical hemorrhage and upper gastrointestinal hemorrhage.[9] Moreover, recent studies have indicated that ABO blood type system exerts the significant impact on hemostasis due to the association with plasma levels of the procoagulant protein factor VIII (FVIII) and von Willebrand factor (vWF).[10] Levels of FVIII and vWF were significantly decreased in individuals with blood type O. And, blood type O was also proved to be a potentially important risk factor for bleeding.[11] However, a recent study showed an association between blood type B and hematoma expansion,[12] not consistent with previous researches. That study extended the time of baseline computed tomographic (CT) to 24 hours after symptoms onset, actually, hematoma expansion often occur within the first few hours after stroke,[4] and most studies limited the time within 6 hours.[13-16] Hematoma expansion may already occur between 6 hours and 24 hours after symptoms onset, which may lead to potential selection bias.

The purpose of this study was to evaluate the association of blood type O with hematoma expansion in the early phase. Our hypothesis is that patients with blood type O are more likely to develop hematoma expansion, and blood type possibly serves as a clinically useful method to predict patients who will suffer hematoma expansion.

Materials and Methods

Study Design and Patient Selection

Patients aged more than18 years with ICH admitted to our institution and underwent baseline and follow-up CT scan between June 2015 and June 2018 were identified retrospectively. Patients diagnosed with spontaneous ICH on noncontrast CT within 6 hours after symptoms onset, and follow-up CT available within 48 hours after the baseline CT scan were included. Exclusion criteria were as follows: (1) ICH caused by traumatic brain injury, cerebral aneurysm, arteriovenous malformation, brain tumor stroke, or hemorrhagic transformation of ischemic stroke, (2) primary intraventricular hemorrhage, (3) surgical evacuation of hematoma before the follow-up CT scan, (4) receiving anticoagulant or antiplatelet therapy before symptoms onset, and (5) blood type not available. Target systolic blood pressure goal was less than 140 mmHg during the first 24 hours after admission, administered with continuous urapidil infusion, according to the guidelines.[17] The demographic information and time to baseline and follow-up CT scans were collected for each individual. This study was approved by the institutional review board of The Second Affiliated Hospital of Chongqing Medical University and the board waived the need for patient consent.

Imaging Analysis

The baseline and follow-up CT scans were obtained using an axial technique with standard clinical parameters and 5-mm section thickness reconstruction. The hematoma volume was calculated using ABC/2 method based on ellipsoid volume formula.[18] Hematoma expansion was defined as a relative volume increase more than33% from baseline ICH volume or an absolute volume increase more than6 mL according to previous definitions.[14,19,20]

Clinical Date

The blood type is a routine examination of all ICH patients admitted in case of surgery. Demographic and clinical data were collected at baseline included age, sex, smoking, and past medical history of hypertension, and diabetes mellitus. Time from symptom onset to baseline CT scan, ICH locations, admission Glasgow Coma Scale (GCS) score, systolic and diastolic blood pressure, hemoglobin (Hb), international normalized ratio (INR), activated partial thromboplastin time (APTT), platelet (PLT) count, and blood type (A, B, AB, or O) were also documented.

Statistical Analysis

Continuous variables with normal distributions were expressed as mean ± SD. When it comes to skewed distributions, the median and the interquartile range (IQR) for each variable were calculated. Categorical variables were presented as percentages. The demographic, clinical, and imaging characteristics were compared between patients with and those without hematoma expansion by using the χ^2 test, the t test, or the Mann-Whitney U test as appropriate. Then, patients were divided into 4 groups by blood type (O, A, B, and AB). The differences among the 4 groups were determined applying one-way analysis of variance. Further analysis was performed to assess the difference between blood type O and non-O blood type. Univariable and multivariable logistic regression models assessed the associations of baseline characteristics with hematoma expansion. All variables with $P < .10$ in the univariable analysis were included in the multivariable logistic regression model. And the multivariable logistic regression was performed to evaluate the association of the blood type O and hematoma expansion. Sensitivity, specificity, positive predictive value, and negative predictive value in predicting hematoma expansion were presented. All statistics and plots were performed by using SPSS 19.0 software and $P < .05$ was considered to be statistically significant.

Results

Baseline Characteristics

After application of the inclusion and exclusion criteria, 210 of 383 patients with ICH were included in the analysis (Fig 1). There were 72 women and 138 men. The mean age of the patients was 59.7 ± 13.8 years. The median time from symptom onset to baseline CT scan was 2 (IQR, 2-5) hours. The median baseline hematoma volume was 14.5 mL (IQR, 5-27 mL), and 61 patients (29.0%) had

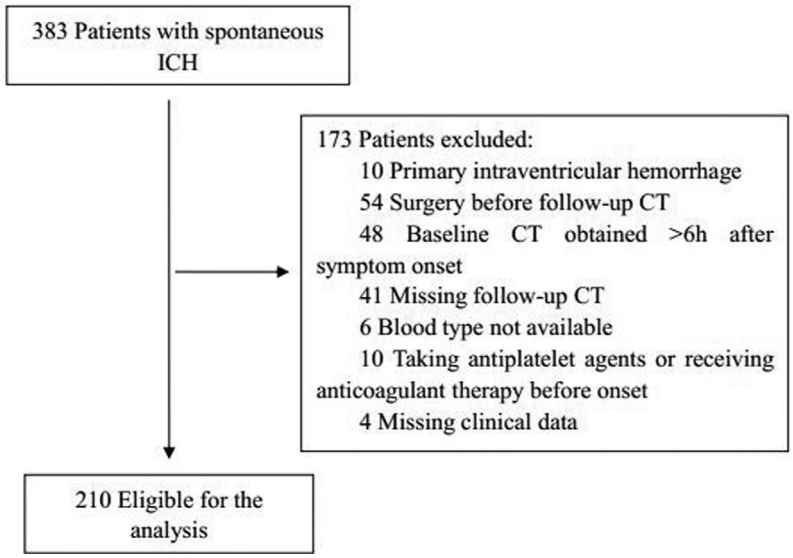

Figure 1. *Study flowchart.*

intraventricular hemorrhage on the baseline CT scan. A total of 55 patients (26.2%) with ICH developed significant hematoma expansion. The baseline clinical characteristics of individuals with and without hematoma expansion were compared and listed in Table 1. Patients with hematoma expansion were more likely to have lower GCS score, shorter time to baseline CT scan, and larger baseline hematoma volume ($P < .05$). In addition, the blood type O was more common in patients with hematoma expansion (54.5%) than those without hematoma expansion (27.1%; $P < .001$). There were no statistically significant differences in sex, age, smoking, hypertension, diabetes mellitus, blood pressure, intraventricular hemorrhage, ICH locations, Hb, PLT count, APTT, and INR ($P > .05$).

Blood Type

We observed 72 patients (34.3%) carrying blood type O, of whom 30 patients (41.7%) developed hematoma expansion. Of 138 patients with other blood types, 16 patients carrying

Table 1. *Comparison of baseline demographic and clinical characteristics between patients with and without hematoma expansion*

	Hematoma expansion		
	Yes (n = 55)	No (n = 155)	*P* value
Male, n (%)	40 (72.7)	98 (63.2)	.202
Age, mean (SD)	60.8 (12.8)	59.3 (14.1)	.510
Smoking, n (%)	26 (47.3)	71 (45.8)	.851
Hypertension, n (%)	47 (85.5)	130 (83.9)	.782
Diabetes mellitus, n (%)	6 (10.9)	12 (7.7)	.660
SBP on admission, mmHg, mean (SD)	173 (23.3)	172.9 (30.2)	.981
DBP on admission, mmHg, mean (SD)	102.5 (17.6)	100.3 (18.4)	.437
GCS score, median (IQR)	12 (9-14)	14 (12-15)	<.001
Intraventricular hemorrhage, n (%)	16 (29.1)	45 (29.0)	.993
Time to baseline CT scan, h, median (IQR)	2 (1-2)	3 (2-5)	<.001
Baseline hematoma volume, mL, median (IQR)	20 (9-30)	10 (5-24)	<.001
ICH locations			.905
Infratentorial, n (%)	5 (9.1)	16 (10.3)	
Lobar, n (%)	12 (21.8)	37 (23.9)	
Deep, n (%)	38 (69.1)	102 (65.8)	
Hb, g/L, median (IQR)	143 (130-155)	141 (127-149)	.207
PLT count, 1000 cells/μL, mean (SD)	178.8 (67.7)	193.3 (57.2)	.124
APTT, s, median (IQR)	35.1 (33.6-38.4)	34.9 (32.4-37.4)	.360
INR, median (IQR)	1.03 (0.98-1.09)	1.02 (0.97-1.08)	.650
Blood type O, n (%)	30 (54.5)	42 (27.1)	<.001

Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PLT, platelet; SBP, systolic blood pressure; SD, standard deviation.

Table 2. *Comparison of baseline demographic and clinical characteristics in each blood type*

	Type O n = 72	Type A n = 77	Type B n = 45	Type AB n = 16	*P* value
Male, n (%)	49 (68.1)	54 (70.1)	26 (57.8)	9 (56.3)	.434
Age, mean (SD)	58.3 (13.9)	61.0 (14.5)	58.4 (12.4)	63.7 (13.3)	.369
Smoking, n (%)	32 (44.4)	39 (50.6)	19 (42.4)	7 (43.8)	.795
Hypertension, n (%)	60 (83.3)	65 (84.4)	37 (82.2)	15 (93.8)	.735
Diabetes mellitus, n (%)	3 (4.2)	9 (11.7)	4 (8.9)	2 (12.5)	.383
SBP on admission, mmHg, mean (SD)	171.8 (29.4)	172.3 (27.1)	172.6 (29.9)	182.0 (27.8)	.621
DBP on admission, mmHg, mean (SD)	101.9 (19.3)	99.5 (18.7)	99.9 (16.8)	105.4 (13.8)	.615
GCS score, median (IQR)	12.5 (10-14)	13 (10-15)	14 (12.5-15)	14 (12.3-15)	.075
Intraventricular hemorrhage, n (%)	22 (30.6)	22 (28.6)	13 (28.9)	4 (25.0)	.975
Time to baseline CT scan, h, median (IQR)	2 (2-4)	3 (1.5-5)	2 (1-5)	4 (2.3-5)	.375
Baseline hematoma volume, mL, median (IQR)	15 (5.3-27)	18 (7-30)	10 (5-20)	7 (3.3-15.8)	.115
ICH locations					.808
Infratentorial, n (%)	5 (6.9)	8 (10.4)	5 (11.1)	3 (18.8)	
Lobar, n (%)	18 (25.0)	19 (24.7)	10 (22.2)	2 (12.5)	
Deep, n (%)	49 (68.1)	50 (64.9)	30 (66.7)	11 (68.8)	
Hb, g/L, median (IQR)	140 (131-148)	142 (126-150)	142 (129-158)	140 (113.5-152.3)	.284
PLT count, 1000 cells/μL, mean (SD)	187.9 (63.4)	186.6 (58.2)	201.8 (60.4)	175.3 (52.2)	.392
APTT, s, median (IQR)	35.2 (33.1-39.0)	35.1 (32.7-37.3)	34.7 (31.9-37.0)	34.6 (31.6-37.2)	.302
INR, median (IQR)	1.03 (0.99-1.10)	1.01 (0.97-1.10)	1.03 (0.99-1.09)	1.04 (0.98-1.06)	.627

Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PLT, platelet; SBP, systolic blood pressure; SD, standard deviation.

blood type AB (7.6%), 77 patients carrying blood type A (36.7%), and 45 patients carrying blood type B (21.4%). Intergroup differences were shown in Table 2. No significant difference was observed in baseline characteristics across blood groups. The baseline imaging and clinical variables of patients with blood type O and other blood types were compared and listed in Table 3. The sex, age, smoking, hypertension, diabetes mellitus, blood pressure, intraventricular hemorrhage, time to baseline CT scan, baseline hematoma volume, ICH locations, Hb, PLT count, APTT, and INR did not differ significantly between patients with blood type O and those with other blood types ($P > .05$). The baseline GCS score of patients with blood type O was lower compared with other blood types ($P = .03$).

Predictors of Hematoma Expansion

In univariate logistic analysis, shorter time to baseline CT scan, larger baseline hematoma volume, lower baseline GCS score, and blood type O were associated with hematoma expansion (Table 4) and were retained in the multivariable logistic regression model. All but baseline hematoma volume remained significant in multivariable analysis (Table 5). The blood type O was an independent predictor of hematoma expansion (odds ratio, 3.15; 95% confidence interval, 1.55-6.41; $P = .002$) and the sensitivity of blood type O for predicting hematoma expansion was 54.5%, specificity 72.9%, positive predictive value 41.6%, and negative predictive value 81.9%.

Discussion

Our results indicated that the blood type O was independently associated with hematoma expansion. Moreover, the blood type could be identified easily and is specific for predicting hematoma expansion. This study also revealed that patients with blood type O had a significantly lower GCS score compared with those with other blood types. Although we cannot alter the risk of blood type O itself, an adequate recognition of the risk enables us to pay more attention to ICH patients with blood type O. These results suggest that blood type may play an essential role in hemostasis with important clinical significance and potential therapeutic implications.

Although the mechanisms underlying the association between blood type and hematoma expansion were not clarified in our study, a number of previous studies have proved that ABO blood type played a potential role for in platelet adhesion, coagulation, and hemostasis. The ABO blood type has been reported as a major determinant of plasma vWF level.[21] Compared with other blood types, patients with blood type O have 25%-30% lower plasma vWF level, which increase the risk of hemorrhage.[11,22] By mediating the adhesion of platelets to the damaged vessel walls and promoting the accumulation of activated platelets, vWF plays an essential role in initial step of hemostatic process. In addition, vWF also acts as a carrier of procoagulant FVIII clotting activity, thereby protects it from premature proteolysis and localize FVIII to the site

Table 3. *Comparison of baseline demographic and clinical characteristics between patients with blood type O and other blood types*

	Blood type O		
	Yes (n = 72)	No (n = 138)	*P* value
Male, n (%)	49 (68.1)	89 (64.5)	.606
Age, mean (SD)	58.3 (13.9)	60.5 (13.7)	.273
Smoking, n (%)	32 (44.4)	65 (47.1)	.714
Hypertension, n (%)	60 (83.3)	117 (84.8)	.784
Diabetes mellitus, n (%)	3 (4.2)	15 (10.9)	.100
SBP on admission, mmHg, mean (SD)	171.8 (29.4)	173.5 (28.1)	.670
DBP on admission, mmHg, mean (SD)	101.9 (19.3)	100.3 (17.6)	.547
GCS score, median (IQR)	12.5 (10-14)	14 (11-15)	.033
Intraventricular hemorrhage, n (%)	22 (30.6)	39 (28.3)	.728
Time to baseline CT scan, h, median (IQR)	2 (2-4)	3 (1-5)	.485
Baseline hematoma volume, mL, median (IQR)	15 (5.3-27)	14 (5-25.3)	.439
ICH locations			.553
Infratentorial, n (%)	5 (6.9)	16 (11.6)	
Lobar, n (%)	18 (25.0)	31 (22.5)	
Deep, n (%)	49 (68.1)	91 (65.9)	
Hb, g/L, median (IQR)	140 (131-148)	142 (126-153)	.826
PLT count, 1000 cells/μL, mean (SD)	187.9 (63.4)	190.3 (58.9)	.788
APTT, s, median (IQR)	35.2 (33.1-39.0)	34.8 (32.4-37.2)	.104
INR, median (IQR)	1.03 (0.99-1.10)	1.02 (0.97-1.07)	.308

Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PLT, platelet; SBP, systolic blood pressure; SD, standard deviation.

of injured vessel.[9,21,23] Therefore, a lower vWF level may be an explanation for the more hematoma expansion in patients with blood type O revealed in our study. Furthermore, in a prospective study of 82 patients, Geoffrey et al[24] identified vWF as a potential predictor of hematoma expansion in patients with ICH through genomic analysis. Our findings were also consistent with previous observations of Wataru Takayama et al,[9] who reported the strong correlation between blood type O and high mortality in severe trauma patients as a result of hemostatic disorders and hemorrhage. Reversely, a previous research revealed having type-B blood increased risk of hematoma expansion.[12] It may be that individuals with blood type O may suffer hematoma expansion before baseline CT, which was scanned within 24 hours after symptoms onset. Additionally, in that study patients with blood type B had more deep primary ICH, shorter time to baseline CT and higher blood pressure, which may lead to hematoma expansion.[17,25] But these crucial variables were not included in the multivariable logistic regression

Table 4. *Univariate analysis of predictors for hematoma expansion*

	OR	95% Wald CI	*P* value
Male	1.55	0.79-3.05	.204
Age	1.01	0.99-1.03	.508
Smoking	1.06	0.57-1.97	.851
Hypertension	1.13	0.48-2.68	.782
Diabetes mellitus	1.46	0.52-4.10	.473
SBP on admission	1.00	0.99-1.01	.983
DBP on admission	1.01	0.99-1.02	.435
GCS score	0.80	0.71-0.90	<.001
Intraventricular hemorrhage	1.00	0.51-1.97	.993
Time to baseline CT scan	0.56	0.44-0.71	<.001
Baseline hematoma volume	1.02	1.00-1.04	.042
ICH locations	1.11	0.69-1.78	.667
Hb	1.01	1.00-1.04	.151
PLT count	1.00	0.99-1.00	.125
APTT	1.01	0.95-1.08	.676
INR	0.86	0.42-1.75	.668
Blood type O	3.23	1.71-6.11	<.001

Abbreviations: APTT, activated partial thromboplastin time; CI, confidence interval; CT, computed tomography; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; Hb, hemoglobin; INR, international normalized ratio; OR, odds ratio; PLT, platelet; SBP, systolic blood pressure.

Table 5. *Multivariate analysis of predictors for hematoma expansion*

	OR	95% Wald CI	*P* value
GCS score	0.86	0.75-0.98	.028
Time to baseline CT scan	0.57	0.44-0.74	<.001
Baseline hematoma volume	1.00	0.98-1.03	.794
Blood type O	3.15	1.55-6.41	.002

Abbreviations: CI, confidence interval; CT, computed tomography; GCS, Glasgow Coma Scale; OR, odds ratio.

model. Further study is required to explore the association of blood type with hematoma expansion in ICH patients.

Hematoma expansion may occur in a cascaded mode, with initial bleeding causing secondary mechanical disruption of neighboring vasculature responsible for ongoing bleeding.[16,26,27] Such expansion may occur in up to 30% of ICH patients and is associated with significantly worse clinical outcomes.[28] Therefore, prevention of hematoma expansion could be a meaningful strategy to restrict the mass effect and secondary brain injury.[29] Agents that affect the coagulation and fibrinolysis status have been investigated. Hematoma expansion could be reduced by administration of hemostatic therapies with factor VIIa[30] or tranexamic acid,[31] however, with no improvement in functional outcome. One possible explanation is that the use of factor VIIa may increase rate of thromboembolic complications.[32] Our study implicate that there may be another opportunity for early interventions to improve hemostasis through vWF administration.

On the other hand, individuals at high risk for hematoma expansion may benefit from administration of hemostatic agents.[33] So, there is an urgent need for biomarkers that can be used to select patients and guide interventions that limit hematoma expansion. In recent years, novel imaging[2,16] and biochemistry[13,15,34] characteristics have been developed for predicting hematoma expansion. Recent studies have identified the presence of contrast extravasation on computed tomographic angiography (CTA) as a promising predictor for hematoma expansion. The PREDICT study, evaluating the accuracy of the CTA spot sign for predicting hematoma expansion, reported a sensitivity of 51%, a specificity of 85%, and positive and negative predictive values of 61% and 78%.[19] In the present study, the sensitivity, specificity, positive, and negative predictive values of blood type O for predicting expansion were 54.5%, 72.9%, 41.6%, and 81.9%, respectively. Although the specificity of blood type O is lower compared with the CTA spot sign, the blood type O is more sensitive for predicting hematoma expansion. Furthermore, CTA is not available or routinely used at all hospitals in the acute situation,[35] while blood type is a cheap, fast, and widely available biomarker. It may be that, ICH patients with blood type O should receive aggressive therapies such as hemostatic drugs and intensive blood pressure reduction just for those patients at higher risk for hematoma expansion. In addition, blood type may help us choose the level of care for patients with ICH.

Some limitations of this study should be considered. First, this was a single-center retrospective study with a limited sample size, so the findings will require replication in other centers. Second, we might underestimate hematoma expansion in small ICH by using 5-mm slice thickness CT scan because of partial volume effect. Third, a part of the subjects with large baseline ICH volume were excluded because of missing follow-up CT for surgery, introducing a potential bias.

In conclusion, blood type O is associated with higher risk of hematoma expansion in patients with ICH. The blood type could be easily identified and is highly sensitive for predicting hematoma expansion. These findings also highlight the role of blood type in coagulation system after ICH and provide a possible opportunity for identification and treatment of patients at high risk of hematoma expansion in clinical practice.

Disclosure

None.

Conflict of Interest

The authors declared that they have no conflicts of interest to this work.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.05.022.

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