CASE-CONTROLLED STUDY OF ACUTE NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING-INDUCED COAGULATION DYSFUNCTION

Ya Zhang[1#], Yu Zhang[2#], Qi Liu[1*], Hong Yang[1], Xian Cao[3]
[1]Department of Gastroenterology, the Affiliated Hospital of Guizhou Medical University, the Affiliated Jingyang Hospital of Guizhou Medical University, Guiyang 550004, China - [2]Department of Digestive Nephropathy, Longshan People's Hospital of Hunan Province, Xiangxi Tujia and Miao Autonomous Prefecture 416800, China - [3]Department of Gastroenterology and Hepatobiliary, the Affiliated Baiyun Hospital of Guizhou Medical University, Guiyang 550058, China
[#]*Co-first authors.*

ABSTRACT

Objective*: To investigate whether coagulation dysfunction exists in patients with acute non-variceal upper gastrointestinal bleeding (ANVUGIB) and whether there may be any change in the coagulation function when the Rockall scores are different.*

Methods*: A total of 364 ANVUGIB patients were selected and divided into the high-risk group (≥5 points, H), the intermediate-risk group (3-4 points, I), and thelow-risk group (0-2 points, L) according to the Rockall scores. The coagulation/fibrinolysis markers were detected in all participants, together with healthy controls selected during the same period.*

Results*: In general, the differences in prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), D-dimer (D-D), and Ca^{2+} between ANVUGIB patients and healthy controls were statistically significant (P<0.05). There was statistical significance in PT, INR, APTT, and Ca^{2+} among the groups with different Rockall scores (P<0.05). There was a negative correlation between Ca^{2+} and Rockall score in group L (P<0.05, r=-0.196) while a positive correlation between D-D and Rockall score in group H (P<0.05, r=0.509).*

Conclusions*: PT, INR, APTT, FIB, D-D, and Ca^{2+}, which are commonly used in laboratory, can be used as effective markers for the diagnosis and treatment of patients with ANVUGIB-caused coagulopathy.*

Keywords: *Acute non-variceal upper gastrointestinal bleeding, Coagulation dysfunction, Rockall score.*

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Introduction

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is one of the most common and critical diseases in clinic with a very high morbidity and mortality[1-3]. ANVUGIB often appears with acute onset and rapid progression, some severe patients may complicate with the life-threatening conditions, like, hemorrhagic shock. In recent years, some risk scores targeting the severity and prognosis of ANVUGIB have been developed, among which the clinical value of the Rockall score[4] has achieved widely recognition. This scoring method includes three clinical indicators (age, shock state, and combined disease) and two endoscopic indicators (endoscopic diagnosis and endoscopic bleeding signs), and divides such patients into the high-risk group, the intermediate-risk group, and the low-risk group. Studies have shown that the Rockall score can better assess the risk of death and rebleeding in patients with ANVUGIB[5,6]. Peptic ulcer is the most common cause of ANVUGIB. Sung et al.[7] retrospectively analyzed the patients with peptic ulcer bleeding and found that most patients did not die of ulcer bleeding itself but the complicated diseases, such as, cerebral infarction, myocardial

infarction or multiple organ failure; the patients with cerebral infarction, myocardial infarction, or multiple organ failure normally have changes in coagulation/fibrinolytic system, so discovering the coagulation changes in such patients timely to guide the precise clinical treatment will be of great importance to reduce the rates of disability and lethality caused by upper gastrointestinal bleeding. Systematic study on the changes in coagulation function of ANVUGIB has been reported only once so far[8], in which a healthy control group was lacking and only one indicators (the International Normalized Ratio, INR) was used to assess the coagulopathy, so it can't fully reflect the changes in coagulation/fibrinolytic system. Therefore this study aims at exploring whether ANVUGIB patients with different Rockall classifications may combine with coagulopathy to provide theoretical basis for better prevention and treatment of such disease.

Material and methods

General information

364 patients with gastrointestinal bleeding were retrospectively selected from the Department of Gastroenterology in the Affiliated Hospital of Guizhou Medical University and the Affiliated Baiyun Hospital of Guizhou Medical University, between January 2013 and December 2015. All the patients were not given any related treatment in the emergency department and directly transferred into the Department of Gastroenterology, completing the endoscopy within 24 hours of onset, and clearly diagnosed as ANVUGIB by endoscopy, excluding those patients combined with cirrhosis, severe liver and renal dysfunction, previous blood disease, severe coagulation disorder that may affect the coagulation function. The patients' clinical data, vital signs on admission, and endoscopic findings were collected based on the Rockall scoring criteria[4] (Table 1) to calculate the Rockall score. The patients were divided into 3 groups according to their individual Rockall score: the high-risk group (≥5 points, H, 61 cases), the intermediate-risk group (3-4 points, I, 119 cases), and the low-risk group (0-2 points, L, 184 cases). At the same period, 99 healthy check-up people were selected as the control group (C), who had no obvious symptoms related the digestive system or hemorrhagic and thrombotic disease. All the participants did not use blood products or any drugs that may affect the blood coagulation function in the past one week. There was no significant difference in the gender and age among the groups (P>0.05). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guizhou Medical University. Written informed consent was obtained from all participants.

Variables	0 point	1 point	2 points	3 points
Age (years)	<60	60–79	≥80	-
Shock state	N[a]	Tachycardia[b]	Hypotension[c]	-
Complications	N	-	Heart failure, ischemic heart disease and other important complications	Liver failure, renal failure, and tumor dissemination
Endoscopic diagnosis	No lesion, Mallory-Weiss syndrome	Ulcer or other diseases	Malignant diseases in the Upper digestive tract	-
Endoscopic bleeding signs	N or black dots	-	Blood retention or adhesion of blood clots as well as blood vessel exposure or blood ejection in the Upper digestive tract	-

Table 1: Rockall scores.

Note: [a]SBP >100mmHg (1mmHg = 0.133kPa), heart rate <100 beats/min; [b]SBP >100mmHg, heart rate >100 beats/min; [c]SBP <100mmHg, heart rate >100 beats/min; Mallory-Weiss Syndrome: esophageal mucosal tearing syndrome; the scoring range is 0-11 points, ≥5 points is defined as the high-risk, 3-4 points is defined as the intermediate-risk, 0-2 points is defined as the low-risk.

Preliminary examination and treatment

The body temperature, pulse, respiratory rate, blood pressure, urine output, and mental changes of the 364 ANVUGIB patients were monitored immediately on admission; meanwhile, all the patients were established the intravenous access for fluid infusion and early application of proton pump inhibitor (PPI) to inhibit bleeding; Gastroscopy was completed within 24 hours for the clear diagnosis.

Laboratory examination

Each patient was sampled 2 ml of peripheral venous blood with 3 tubes immediately on admission. The first blood sample (1.8 ml) was stored in the tube with 0.2 ml of 3.2% (w/v) sodium citrate anticoagulant, followed by mixing and immediately detecting the plasma prothrombin time (PT), INR, activated partial thromboplastin time (APTT), Thrombin time (TT), Fibrinogen (FIB), and D-dimer (D-D) using STA-R Evolution automated coagulation analyzer (STA-R Evolution® automated coagulation analyzer, STAGO Co., France). The second blood sample was stored and mixed in one EDTA anticoagulant tube, and immediately detecting the platelet count (PLT) by BC6900 whole blood cell analyzer (Mindray Co., Shenzhen, China) after mixing. The third blood sample was stored in one anticoagulant-free vacuum tube and immediately testing the Ca^{2+} concentration using the ADVIA2400 automatic biochemical analyzer (ADVIA® 2400 automatic biochemical analyzer, Siemens Co., Germany). The control group was healthy check-up people who were sampled the fasting blood in the morning on the day of physical examination, and the specific methods of taking blood and detecting indicators were the same as above.

Statistical analysis

SPSS14.0 software was used for the statistical analysis; the measurement data in line with the normal distribution were expressed with x-bar ±s and the comparison of the mean of two independent samples used the t-test. The differences among groups were compared using analysis of variance, among which LSD was used for the pairwise comparison, with P<0.05 considered as statistical significance. The Pearson correlation analysis was used to analyze the correlation between the clinical markers of coagulation function and the Rockall score.

Results

Comparison of general information

Table 2 .docx shows that there is no statistical significance in the gender and age between the ANVUGIB patients and the healthy controls (P>0.05).

General information	Group C	H	I	L	*P*
Gender (M/F)	60/39	39/22	66/53	104/80	>0.05
Age (years)	51.55±14.23	58.97±16.84	55.90±14.93	53.64±13.09	

Table 2: Comparison of general information ($\bar{x}$±s).

Comparison of coagulation changes between the experimental group and the control group

As shown in Table 3 .docx.docx, there is statistical significance in the levels of PT, INR, APTT, FIB, D-D, and Ca^{2+} between the ANVUGIB patients and the healthy controls.

Group	N (D-D)	PT (s)	INR	APTT (s)	TT (s)	FIB (g/l)	D-D (μg/l)	PLT (×10⁹)	Ca^{2+} (mmol/l)
ANVUGIB	364 (86)	13.72±1.63[c]	1.05±0.18[c]	35.93±7.64[c]	17.35±2.08	2.72±1.13[c]	2.21±3.34[c]	192.42±89.28	2.06±0.23[c]
C	99 (20)	12.85±0.93	0.96±0.09	38.16±6.17	17.42±2.04	2.90±0.66	0.42±0.29	193.27±50.32	2.37±0.21

Table 3: Comparison of coagulation changes between the experimental group and the control group ($\bar{x}$±s).

*Note: *Compared with group C, P<0.05.*

Coagulation changes and Rockall classification

As shown in Table 4, the levels of PT, INR, D-D in group L are significantly higher while the level of Ca^{2+} is lower than Group C (*P*<0.05), so the difference between group L and group C is statistical significance (*P*<0.05).There is statistical significance in PT, INR, APTT, D-D, and Ca^{2+}between group H, group I and group C (P<0.05). Comparing with group L, the levels of APPT and Ca^{2+} in group I show statistical significance (*P*<0.05). The levels of PT, INR, and Ca^{2+} in group H show statistical significance when comparing with group L (*P*<0.05); PT and INR in group H are more significantly prolonged than group I, and the differences are statistically significant (P<0.05).

Group	PT	INR	APTT	TT	FIB	D-D	PLT	Ca^{2+}
L	-0.023	-0.001	-0.084	-0.040	0.065	0.210	-0.092	-0.196[*]
I	0.111	0.094	-0.122	0.148	-0.120	0.337	-0.046	-0.077
H	0.156	0.149	0.160	0.097	-0.103	0.509[a]	0.012	-0.103

Table 4: Comparison of coagulation function among groups ($\bar{x}$±s).

Note: [a]compared with group C, P<0.05; [b]compared with group L, P<0.05; [c]compared with group I, P<0.05.

Correlation analysis of PT, INR, APTT, TT, FIB, D-D, Ca2+, and PLT with Rockall score

As shown in Table 5 .docx, there is a negative correlation between Ca^{2+} and the Rockall score in group L (P<0.05, r=-0.196). D-D is positively correlated with the Rockall score in group H (*P*<0.05, r=0.509).

Group	N (D-D)	PT (s)	INR	APTT (s)	TT (s)	FIB (g/l)	D-D (μg/l)	PLT (×10⁹)	Ca^{2+} (mmol/l)
L	184 (35)	13.58±1.30[a]	1.04±0.16[a]	36.66±8.93	17.52±2.17	2.74±1.18	2.08±3.61[a]	199.22±88.79	2.10±0.20[a]
I	119 (27)	13.57±1.96[a]	1.04±0.16[a]	34.99±5.31[ab]	17.11±1.86	2.69±1.09	2.03±2.63[b]	186.16±82.41	2.02±0.25[ab]
H	61 (24)	14.38±1.69[abc]	1.10±0.24[abc]	35.52±7.16[a]	17.34±2.21	2.72±1.07	2.62±3.74[a]	185.31±102.81	2.02±0.24[ab]
C	99 (20)	12.88±0.93	0.96±0.09	38.16±6.17	17.42±1.92	2.88±0.66	0.42±0.29	192.60±50.32	2.37±0.21

Table 5: Correlation analysis of coagulation indicators with Rockall score among different groups.

*Note: *P<0.05.*

Discussion

So far, systematic studies targeting the coagulation disorders caused by ANVUGIB are still rare, but patients with upper gastrointestinal bleeding combined with coagulopathy are common in clinic, and they often have critical diseases and poor prognosis. It has been found that most patients with peptic ulcer bleeding do not die of ulcer bleeding itself but the complicated diseases, such as, cerebral infarction, myocardial infarction, or multiple organ failure[7]. From the pathophysiological point of view, it can be reasonably speculated that patients with upper gastrointestinal bleeding are normally combined with cerebral infarction, myocardial infarction, or abnormal coagulation function. In order to prevent and reduce such lethal causes as far as possible, it will have positive clinical significance for studying the coagulation dysfunction caused by ANVUGIB.

In recent years, acute coagulation dysfunction after trauma has become a hot issue in international research because of the commonness and high mortality of hemorrhage and coagulopathy in trauma. Throughout its pathogenesis and pathophysiological processes, it is not difficult to find that the ANVUGIB-caused coagulation disorders exhibit certain similarities. Acute traumatic coagulopathy (ATC) is an early endogenous coagulation disorder driven by tissue injury and shock[9,10]. A large number of studies[11-13] have confirmed the impact of the six factors, namely tissue injury, hypoperfusion,

hemodilution, hypothermia, acidosis, and inflammation, to be the "initiator" of ATC.

The main mechanism of ATC is the damage of endothelial cell activates the protein C (APC)[14-16], which further inhibits the V and VIII coagulation factors, and the amounts of proteoglycan-1 and glycoproteins on the endothelial cell surface are significantly increased[17]; meanwhile, a large number of antithrombin III can be released[18], which further promotes the body's anticoagulant activity[19] while inhibits the formation of thrombin, thus further inducing hyperfibrinolysis. With the development of disease, patients with traumatic shock may further aggravate coagulation disorders due to hemodilution, hypothermia, or acidosis caused by liquid resuscitation, so the rapid and accurate detection of coagulation disorders is particularly important.

It is well known that the mechanisms of normal coagulation and hemostasis depend on the integrity of vascular walls, platelets, clotting factors, anticoagulants, fibrinolytic system, and hemodynamics, as well as the physiological balance among them. The coagulation pathways can be divided into three: one is the endogenous coagulation pathway, mainly initiated by the coagulation factor XII; the second one is the extrinsic coagulation pathway, mainly depending on the tissue factor (TF) for the start; the third one is the common pathway of the first and second. PT, INR, APTT, TT, FIB, and D-D are commonly used indicators in clinic to test the coagulation function. Considering PT and APTT as sensitive indicators that can respectively reflect the extrinsic and intrinsic coagulation pathways, platelets play a key role in the process of coagulation, and Ca^{2+} acts as the initiating factor of the extrinsic coagulation pathway. Therefore, the above indicators were selected for the test in this study.

The study found that all the ANVUGIB patients showed statistical significance in PT, INR, APTT, FIB, DD, and Ca^{2+} when comparing with healthy controls, thus confirming the existence of coagulation disorders in ANVUGIB patients, the reasons in the early stage may be: 1) bleeding leads to the decrease of the blood volume, which directly causes the loss of clotting factors; the start of the coagulation mechanism after body injury further causes the consumption of coagulation factors in the process of coagulation; 2) insufficient tissue perfusion and acidosis caused by the release of a large number of lactic acid in the anaerobic metabolism can also further aggravate coagulation disorders; the reasons in the late stage and the related mechanisms of ATC as well as fluid resuscitation after admission can further aggravate coagulation disorders.

In this study, according to the Rockall scoring classifications, the levels of PT, INR, APTT, D-D, and Ca^{2+} were different among different groups. PT, INR, and D-D gradually increased while Ca^{2+} gradually decreased from group L to group I and to group H, suggesting that the changes of coagulation parameters PT, INR, D-D, and Ca^{2+} are closely related to the severity of ANVUGIB. Combining the results of this study, it can be confirmed that the dynamic balance of coagulation and fibrinolysis in ANVUGIB is broken, and concluding from the changes in various coagulation indicators, it can be considered that the early blood loss in ANVUGIB can slow down the flow of blood, thus forming small blood clots and causing the hypercoagulable state; later, the large consumption of blood coagulation factors turns the blood from the hypercoagulable state to the hypocoagulable state, which eventually leads to coagulation disorders and even DIC or multiple organ dysfunction (MODS) in severe cases. The PLT in this study showed no statistical significance when comparing with group C. It may be considered similar to the early stage of coagulation changes due to traumatic hemorrhage, during which period the PLT count is within the normal limitation while the platelet function is abnormal[20-22].

Rockall[4] proposed the Rockall scoring criteria in 1996 and classified the patients with ANVUGIB into the low-risk group (0-2 points), the intermediate-risk group (3-4 points), and the high-risk group (≥5 points) based on the age, shock state, combined diseases, endoscopic diagnosis, and endoscopic bleeding signs. As the risk score increases, the rates of rebleeding and mortality become higher, and older patients are more likely to occur rebleeding[5,23]. Thus, it can be seen that the Rockall score evaluation is particularly important for ANVUGIB patients. This study found that the level of Ca^{2+} in group L was negatively correlated with the Rockall score, which means the higher the score, the lower level of Ca^{2+}. The level of D-D was positively correlated with the Rockall score in group H, namely means the higher level of D-D, the higher the Rockall score, and the more severe the disease conditions; however, no significant linear correlation can be found in group L. According to the linear relationship between the changes on the levels of D-D/Ca^{2+} and the Rockall score, whether it can be used to initially judge the prognosis and disease changes and whether it can

provide help for prevention and treatment still needs further studies.

In summary, this study found that patients with ANVUGIB do exist coagulation dysfunction, but the disadvantage of this study was that we didn't review the ANVUGIB patients after treatment nor explore whether there were changes in the blood coagulation after infusion of blood products, or whether the disease duration had certain effects on the coagulation function. However, this was only an early study, our further studies will pay attention to in which stage the coagulation/Fibrinolysis starts, how develop and evolve, when it will be the best time for intervention treatment, and how to interfere the disease so as not to affect the hemostasis while prevent it from developing into irreversible changes. All the above needs a further attention and research.

Conclusions

The commonly used laboratory markers PT, INR, APTT, FIB, D-D, and Ca^{2+} can be used as effective diagnostic indicators for patients with ANVUGIB-induced coagulation disorders, and have important significance for the clinical judgment, treatment guidance, and prognosis evaluation. There are differences in the levels of PT, INR, APTT, and Ca^{2+} among the patients with different Rockall scoring classifications, and there is linear correlation between the levels of Ca^{2+}/D-D and the Rockall score.

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Corresponding Author:
Qi Liu
Department of Gastroenterology,
The Affiliated Hospital of Guizhou Medical University,
Guiyang 550004
Email: qiliucn@126.com
(China)