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New Signaling Systems of Nitric Oxide (No) and Vascular Adhesion Molecule Svcam-1 in the Diagnosis of Recurrent Ulcerative Gastroduodenal Bleeding

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Abstract: In this article, we presented the results of studying the prognostic significance of various clinical, laboratory, endoscopic factors, indicators of the severity of the patient's condition according to APACNE-III, the severity of blood loss and hemorrhagic shock, comorbidity and factors of the blood coagulation system in predicting the risk of bleeding in patients with peptic ulcer complicated by acute gastro-duodenal ulcerative bleeding. In a certain number of patients with acute gastroduodenal ulcerative bleeding, along with quantitative and qualitative risk factors for bleeding, the indicators of NO and sVCAM-1 were studied in a comparative aspect and their correlation was determined.

Keywords: *gastroduodenal ulcer bleeding, recurrence of bleeding, mortality, predictive coefficient, hemorrhagic shock, ulcer, sVCAM-1, NO*

1. Introduction

Owing to the introduction of new antiulcer drugs of the group of proton pump blockers, H2 receptors and anti-Helicobacter therapy, certain successes have been achieved in the treatment of peptic ulcer. But mortality from ulcerative gastroduodenal bleeding remains in the range of 10-14% [15,16]. At the same time, it is known that gastroduodenal bleeding accounts for 42-47% of the structure of complicated forms of peptic ulcers. On the other hand, recurrent bleeding significantly exacerbates primary blood loss, significantly worsening the prognosis of the disease. The inefficiency of endoscopic hemostasis forces doctors to operate on patients at the height of bleeding. The overall mortality in recurrence of acute gastroduodenal ulcerative bleeding (AGDUB) ranges from 15 to 30%, and postoperative mortality reaches up to 40-75% [1,3,4, 5,6,7,13,14].

To reduce the mortality rate in AGDUB, it is necessary to predict the possibility of recurrence of ulcerative bleeding in a timely manner, to determine the correct and optimal tactics for managing patients, hemostasis, indications for surgery with the choice of the optimal volume of surgical interventions. Unfortunately, numerous studies devoted to the study of the prognostic significance of various factors contributing to the recurrence of gastroduodenal ulcerative bleeding are contradictory, since the risk of recurrent bleeding (RB) is not always detected in a timely manner. The resolving signaling ability of many of these factors will not exceed 11.7-33.3%, and the prognostic coefficient (PC) is 0.206-0.750 [2, 6, 8, 9, 10, 11, 12].

As can be seen from the above data, described in the existing literature, numerous methods based on the identification of clinical, endoscopic, laboratory and instrumental signs of hemostasis instability did not solve the problem of early detection of recurrent ulcer bleeding. In this regard, the search for non-cumbersome, but objective criteria for predicting RB, based on pathogenetic mechanisms and characterizing the dynamics of the state of a local pathological condition, such as blood NO, adhesion of vascular molecules, thrombocytopenia, etc., remains relevant.

As is commonly known, the endothelial form of nitric oxide (NO) is synthesized by the tissues of the inner lining of the arteries and plays an important role in the control of blood flow. Another member of the immunoglobulin superfamily, sVCAM-1, provides adhesion of blood cells inside and outside the vessel. In connection with the foregoing, it is of great practical importance to elucidate the role of NO and sVCAM-1 in predicting RB, as objective criteria for predicting the risk of bleeding, which have pathogenetic significance in the development of AGDUB and RB..

2. Material and research methods

We studied the prognostic significance of various clinical, laboratory, endoscopic factors, indicators of the severity of the patient's condition according to APACHE-III, the severity of blood loss and hemorrhagic shock (HS), concomitant pathology and factors of the blood coagulation system in predicting RB in 344 patients with peptic ulcer (PU) complicated by AGDUB (control group). In 52 patients with AGDUB (constituting the main group of the study), along with 34 quantitative and qualitative risk factors for RB, NO and sVCAM-1 indicators were studied in a comparative aspect and their correlation was determined.

Analysis of the obtained data of the control group showed the following indicators:

1) That severe and extremely severe blood loss in 33.1-33.3% of cases leads to RB, PC = 0.750. With mild to moderate blood loss, the probability of RB is small (PC = 0.22 in 6.7% of cases).

2) In the absence of hemorrhagic shock and grade 1 hemorrhagic shock, the probability of RB is negligible (PC=0.004 in 19.1% of cases). The presence of hemorrhagic shock II-III degree significantly increases the likelihood of RB 0.206-0.273 in 27.3-33.3% of cases.

3) With a decrease in blood hematocrit (HT) to 21-30%, the probability of RB reaches 30%, PC=0.206

4) Of the existing comorbidities, diabetes mellitus (PC=0.750 in 33.3% of cases) and arterial hypertension (PC=0.700 in 27.8% of cases) significantly increased the risk of RB.

5) According to the study of indicators APACHE-III (Knauss et all 1981) made it possible to predict RB with a PC of 0.75 in 38.1% of cases.

6) Thrombocytopenia below 150,000 and thrombotest below grade 4 significantly increase the risk of rebleeding (PC=0.813 in 30.7% of cases and PC=0.507-0.907 in 50-75% of cases).

7) Endoscopic studies of patients revealed that the larger the size of the ulcer, the higher the likelihood of developing RB. (When d ulcers are 1.1-2.0 and higher, PC = 0.507-0.900 in 50-75% of cases). There is a high probability of RB in the localization of the ulcer on the posterior wall of the duodenal bulb (PDB) (PC=0.206 in 33.3%), and "kissing ulcers" (PC=0.507 in 50% of cases). The most likely to develop RB were ulcers that had F-1A arterial bleeding (PC=0.890 in 28% of cases) or active venous bleeding F-1B (PC=0.603 in 55.5% of cases) at the time of endoscopic admission.

Below we present the results of studies of the main group.

By studying the indicators of NO and sVCAM-I, in three healthy people, the normal values of NO = 159.6 μmol/l were specified; sVCAM-I = 22.7 ng/ml.

The study of NO and sVCAM-1 in four patients with DU showed a decrease in NO to 42.8 μmol/l; at the same time, some compensatory increase in sVCAM-1 up to 32.0 ng/ml. According to our data, with ulcerative bleeding, NO indicators decrease from 2.5 to 25 times, in direct proportion to the severity of blood loss and the presence of hemorrhagic shock from (4.4 to 22.3 μmol/l) with severe blood loss. Bleeding from combined ulcers was also accompanied by a sharp decrease in NO values to 6.2-6.8 μmol/l. There was no significant dependence of NO reduction on bleeding recurrence. With AGDUB, the sVCAM-1 values also decreased, but to a lesser extent, 2-3 times compared with the norm, and 3-4 times with repeated bleeding.

Primary and repeated indicators of NO and sVCAM-1 in patients with AGDUB, depending on the severity of blood loss and hemorrhagic shock and bleeding recurrence, are shown in tables No. 2-10 separately for patients with gastric ulcer (GU) and duodenal ulcer (DU).

Table 1. Distribution of patients by groups and age

Patient groups	**Age (years and %)**			
	up to 44 years	45-59	60-74	75 years and older
control n=344	152(44,2)	126(36,6)	66(19,2)	-
main n=97 of them	37(38,2)	39(40,2)	14(14,4)	7(7,2)
With determination of NO and sVCAM-1 in serum (n=52 patients)	23(44,2)	18(34,6)	7(13.4)	4(7,7)
With the definition of NO and sVCAM-1 mathematically (n=45 б-х)	14(31,1)	21(46,7)	7(15,5)	3(6,7)
Total n=441	189(42,8)	165(37,4)	80(18,2)	7(1,6)

Note. % is given in parentheses.

In the control group, peptic ulcer was most often complicated by bleeding in patients of the most able-bodied age. In the group of patients under 45 years old - 152 (44.2%), in patients 45-59 years old - 126 (36.6%), in the main group under 45 years old - 37 (38.2%), and in the age of 45-59 years old - 39 (40.2%), which once again underlines the social significance of the problem under study. The least amount of bleeding was noted in patients over the age of 60 years - 66 (19.2%) in the control group and 21 (21.6%) in the main group of patients.

Table 2. Probability of developing gastric RB depending on the severity of bleeding according to NO indicators (primary)

Severity of bleeding	**NO indicators (primary) in patients (μmol/l)**		**Probability RB**	
	without RB p = 8	With RB p = 6	PC	%
mild	38,7 (3)	-		
medium	43,9 (3)	30,2(2)	-0,0375	40,7%
severe	26,6(2)	6.2(4)	-0,507	19%
total	8	6		

Table 3. Probability of developing gastric RB depending on the severity of bleeding according to NO indicators (repeated)

Severity of bleeding	NO indicators (repeated) in patients (μmol/l)		Probability RB	
	without RB p = 8	With RB p = 6	PC	%
mild	102,3 (3)	-		
medium	193,4 (3)	107,5 (2)	0,1301	35,7%
severe	32,5 (2)	59,7 (4)	0,389	64,7%
total	8	6		

Table 4. Probability of developing gastric RB depending on the severity of bleeding according to *sVCAM-1* indicators (primary)

Severity of bleeding	*sVCAM-1* indicators (primary) in patients (ng/ml)		Probability RB	
	without RB p = 8	With RB p = 6	PC	%
mild	12,3 (3)	-		
medium	20 (3)	16 (2)	0,028	44,5%
severe	14 (2)	14,8 (4)	0,149	51,4%
total	8	6		

Table 5. Probability of developing gastric RB depending on the severity of bleeding according to *sVCAM-1* indicators (repeated)

Severity of bleeding	*sVCAM-1* indicators (repeated) in patients (ng/ml)		Probability RB	
	without RB p = 8	With RB p = 6	PC	%
mild	19 (3)	-		
medium	17,3 (3)	15 (2)	0,0629	46,4%
severe	14 (2)	13,8 (4)	0,118	50%
total	8	6		

Table 6. The probability of developing RB DU depending on the severity of bleeding according to NO indicators (primary)

Severity of bleeding	NO indicators (primary) in patients (ng/ml)		Probability RB	
	without RB p = 20	With RB p = 8	PC	%
mild	68,97 (3)	20,9 (2)	0,1205	23,25%
medium	13,25 (9)	55,9 (2)	1,023	80,8%
severe	20,1 (8)	31,2 (4)	0,588	60,8%
total	20	8		

Table 7. The probability of developing RB DU depending on the severity of bleeding according to NO indicators (repeated)

Severity of bleeding	NO values (repeated) in patients (μmol/l)		Probability RB	
	without RB p = 20	With RB p = 8	PC	%
mild	156 (3)	157 (2)	0,4007	50,2%
medium	130,3 (9)	144 (2)	0,441	52,5%
severe	77,7 (8)	113,9 (4)	0,564	59,4%
total	20	8		

Table 8. The probability of developing RB DU depending on the severity of bleeding according to sVCAM-1 indicators (primary)

Severity of bleeding	sVCAM-1 indicators (primary) in patients (ng/ml)		Probability RB	
	without RB p = 20	with RB p = 8	PC	%
mild	23,6 (3)	14,5 (2)	0,186	38%
medium	19,1 (9)	19,5(2)	0,406	50,5%
severe	10,2 (8)	11,5 (4)	0,450	53%
total	20	8		

Table 9. The probability of developing RB DU depending on the severity of bleeding according to sVCAM-1 indicators (repeated)

Severity of bleeding	Indicators of sVCAM-1 (repeated) in patients (ng/ml)		Probability RB	
	without RB p = 20	with RB p = 8	PC	%
mild	21 (3)	20,5 (2)	0,387	50%
medium	16,7 (9)	18 (2)	0,430	50%
severe	15,5 (8)	16,5 (4)	0,425	51,5%
total	20	8		

As can be seen from the tables, NO indicators in AGDUB are significantly reduced and predict the likelihood of RB in gastric localization of an ulcer of moderate and severe blood loss in 19 - 40.7% of cases (NO primary) and 35.7 - 64.7% of cases (NO repeated).

In duodenal ulcer, the probability of RB is predicted in 60.8-80.8% of cases (PC NO primary = 1.023-0.588); and with repeated bleeding of duodenal ulcers in 52.5-59.5% of cases (PC = 0.441-0.564).

Thus, the study of NO is 2-3 times more accurate than the study of hemorrhagic shock, the severity of the degree of blood loss, comorbidity, size and location of ulcers, predicts the likelihood of RB.

The study of indicators of another member of the superfamily of immunoglobulins sVCAM-1 in patients with AGDUB showed a decrease in its indicators in the blood by 2-3 times, with repeated bleeding up to 3-4 times.

Mathematical study of PC and probability RB predicts the probability of RB in 44.5-53% of cases, i.e., 2 times more accurately than with conventional mathematical and integral methods of predicting RB.

Primary and repeated indicators of NO and sVCAM-1 in patients with AGDUB, depending on the severity of blood loss and hemorrhagic shock and recurrence of bleeding, are shown in Table 10 separately for patients with gastric ulcer (GU) and duodenal ulcer (DU). For comparison, APACHE-III indicators are given.

Table 10. The probability of developing AGDUB depending on the severity of blood loss, NO, sVCAM-1 and APACHE-III in the main group.

№	Peptic ulcer degree of blood loss and localization of the ulcer		NO indicators		Probability RB		SVCAM-I indicators and probability RB				APACHE III (total points) and probability RB			
			without RB	with RB	PC	%	without RB	with RB	PC	%	without RB	with RB	PC	%
1	GU n=14	mild	38,7	-	-		12,3	-						
		Medium	43,3	30,2	-0,037	40,7	20	16	0,028	44,5	45,9	37	0,03	44,6

		Severe	26,6	6,2	-0,507	19	14	14,8	0,149	51,4				
2	DU n=28	Mild	68,9	20,9	0,1205	23,4	23,6	14,5	0,186	38	56,6	27	-0,197	32,3
		Medium	13,2	55,9	1,023	80,8	19,1	19,5	0,406	50,5				
		Severe	20,1	31,2	0,588	60,8	10,2	11,5	0,450	53				

Thus, a decrease in NO in blood serum predicts the possibility of RB 2-3 times more accurately, and changes in sVCAM-1 parameters are 2 times more accurate than the existing clinic - laboratory, endoscopic, integral methods and APACHE -III.

3. Conclusions.

1. The presence of heavy bleeding, with the development of hemorrhagic shock II-III st. and at the same time reducing hematocrit to 30% and below the numbers, significantly increases the risk of recurrent bleeding.
2. The presence of severe comorbidities (diabetes mellitus and arterial hypertension) and low APACHE-III levels increase the risk of RB to a large extent.
3. Thrombocytopenia below 150,000 and thrombotest below IV st. increase the risk of RB.
4. Endoscopic data in the form of the presence of large ulcers (d -1.1-2.0 and more), localization of ulcers in the posterior wall of the duodenum bulb or the presence of "kissing ulcers", and pictures F-I A, F-1 B, indicate the possibility RB.
5. The decrease in the new NO signaling system in the blood serum predicts the possibility of RB 2-3 times more accurately than the existing clinical laboratory, endoscopic and integral research methods.

4. References.

[1] Ang D. A comparison of surgery versus transcatheter angiographic embolization in the treatment of nonvariceal upper gastrointestinal bleeding uncontrolled by endoscopy / D. Ang, E.K. Teo, A. Tan et al. // Eur. J. Gastroenterol. Hepatol. - 2012. - V. 24 [8]. - P. 929-938.

[2] Bardou M. Preventing the gastrointestinal adverse effects of nonsteroidal antiinflammatory drugs: from risk factor identification risk factor intervention / M. Bardou, A.N. Barkun // Joint Bone Spine.- 2010.- Vol.77 [1]. - P. 6-12.

[3] Bertleff M.J. Perforated peptic ulcer disease: a review of history and treatment / MJ.Bertleff, J.F. Lange // Dig Surg. - 2010. - Vol.27. - P.161-169

[4] Bini, E.J. Endoscopic treatment compared with medical therapy for the prevention of recurrent ulcer hemorrhage in patients with adherent clots / E.J. Bini, J. Cohen // Gastrointest Endosc. – 2003. – № 58. P. 707–714.

[5] Blatchford O.A risk score to predict need for treatment for upper-gastrointestinal haemorrhage / O.Blatchford, W.R.Murray, M. Blatchford // Lancet.-2010. - Vol.356. - P. 1318-21.

[6] Bobrzynski A., Beben P., Budzynski A. et al. Incidence of complications of peptic ulcers in patients with Helicobacter pylori [Hp] infection and/or NSAID use in the era of Hp eradication // Med. Sc. Monit. - 2002. -№ 8. -P. 554-557.

[7] Broze G.J.Jr. Tissue factor pathway inhibitor and the current concept of blood coagulation. Blood Coagul. Fibrinolysis. 1995; 6 [Suppl 1]: S7-S13. DOI: 10.1097/00001721-199506001-00002. PMID: 7647225.

[8] Button L.A. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study / L.A.Button // Aliment Pharmacol Ther. - 2011. - Vol.33. -P.64-76.

[9] Canoy D.S., Hart A.R., Todd C.J. Epidemiology of duodenal ulcer perforation: a study on hospital admissions in Norfolk, United Kingdom // Dig. Liver Dis.-2012. - Vol. 34, № 5.- P. 322-327.

[10] Chey W.D., Leontiadis G.I., Howden C.W. mss S.F. ACG clinical Guideline: Treatment of helicobacter pylori Infections. Fm. J. Gastroenterol. 2017;112 [2]:212-39.

[11] Chung C.S., Chiang T.H., Lee Y.C. A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers. Korean J Intern Med. 2015; 30(5): 559-70.

[12] Endoscopic factors predisposing to rebleeding following endoscopic hemostasis in bleeding peptic ulcers / I.K. Chung, E.J. Kim, M.S. Lee, H.S. Kim et al. // Endoscopy. – 2011. – № 33. – P. 969–975.

[13] Feinstein L.B. et al. Trends in hospitalizations for peptic ulcer disease, United States, 1998-2005. Emerg Infect Dis. 2010. Vol. 16. P. 1410-1418.

[14] Franzin G., Manfrini C., Musola R. et al. // Endoscopy. 1984. Vol. 16, №1. P. 1-6.

[15] Garrow D. Risk factors for gastrointestinal ulcer disease in the US population / D.Garrow, M.H.Delegge // Dig Dis Sci. - 2010. - Vol.55[1]. -P.66-72.

[16] Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010 / R.Lozano [et al.] // Lancet. - 2012. -Vol.380. - P.2095-2128.

[17] Gosselin R., Adcock D.M., Bates S.M., Douxfils J., Favaloro EJ., Gouin-Thibault I. et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Tromb Haemost. 2018;118(3):437-450. doi: 10.1055/s-0038-1627480.

[18] Hanson S.R., GriffinJ.H, Harker L.A., Kelly A.B., Esmon C.T., Gruber A. Antithrombotic effects of thrombin-induced activation of endogenous protein C in primates. J. Clin. Invest. 1993; 92 [4]: 2003-2012. DOI: 10.1172/JCI116795. PMID: 8408654.

[19] Hoffman M.A., Monroe D.M.3rd. Cell-based model of hemostasis. Thromb. Haemost. 2001; 85 [6]: 958-965. PMID: 11434702.

[20] Hoffman M.A., Monroe D.M.3rd. Cell-based model of hemostasis. Thromb. Haemost. 2001; 85 [6]: 958-965. PMID: 11434702.

[21] Hwang J.H [et al.] The role of endoscopy in the management of acute non-variceal upper GI bleeding // Gastrointest Endosc. - 2012. - Vol.75. - P.1132-1138.

[22] Initial factors predicting rebleeding and death in bleeding peptic ulcer disease / M.H. Al-Akeely, M.K. Alam, S.M. Al-Salamah, M.A. Abdu et al. // Saudi Med J. – 2004. – № 25. – P. 642–647.

[23] Laine L. Management of patients with ulcer bleeding / L.Laine, D.M. Jensen // Am J Gastroenterol.-2012. - Vol.107. - P.345-360.

[24] Laine L. Optimizing bipolar electrocoagulation for endoscopic hemostasis: Assessment of factors influencing energy delivery and coagulation / L. Laine., G.L. Long, G.J. Bakos // Gastrointest Endosc. - 2008. - Vol.67. - P.502-508.

[25] Lau J.Y. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality / J.Y. Lau, J.Sung, C.Hill // Digestion. - 2011. - Vol.84. - P102-113.

[26] Lau J.Y., Sung J., Hill C. et al. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality // Digestion. -2011. -Vol. 84, № 2. -P. 102-113.

[27] Loffroy R. Guiu B. Role of transcatheter arterial embolization for massive bleedingfrom gastroduodenal ulcers. World J. Gastroenterol.2009? 15 [47]: 5889-97.

[28] Nahas L., Macfarlane R.G., Denson K.W. A study of the coagulant action of eight snake venoms. Thromb. Diath. Haemorrh. 1964; 12: 355-367. PMID: 14254694 2] DavieE.W., Ratnoff O.D. Waterfall sequence for intrinsic blood clotting. Science. 1964; 145 [3638]: 1310-1312. DOI: 10.1126/science.145.3638. 1310. PMID: 14173416.

[29] Ohmann C., Imhof M., Ruppert C. et al. Time-trends in the epidemiology of peptic ulcer bleeding // Scand. J. Gastroenterol. -2005. -Vol. 40, № 8. -P. 914-920.

[30] Predicting poor outcome from acute upper gastrointestinal hemorrhage / T.F. Imperiale, et al. // Arch Intern Med.- 2007. - Vol.167. - P.1291-1296.

[31] Rosenstock S.J., Muller M.H., Larsson H., Johnsen S.P., et al. Improving quality of care in peptic ulcer bleeding: nationwide cohor study of 13498 consecutive patients in the Danish clinical Register of Emergency Surgery. Am. Gastroenterol 2013 ; 108 [9]; 1449-57.

[32] Savides T.J. Therapeutic endoscopy for nonvariceal gastrointestinal bleeding / T.J. Savides, D.M. Jensen // Gastroenterol Clin North Am. - 2000. - Vol.29. -P.465-487.

[33] Teles-Sampaio E. Antiplatelet agents and/or anticoagulants are not associated with worse outcome following nonvariceal upper gastrointestinal bleeding / E. Teles-Sampaio, L. Maia, P. Salgueiro et al. // Rev. Esp. Enferm. Dig. - 2016. - V. 108 [11]. -P. 703-708.

[34] Theocharis G., Thomopoulos K., Sakellaropoulos G. et al. Changing trends in the epidemiology and clinical outcome of acute upper gastrointestinal bleeding in a defined geographical area in Greece // J. Clin. Gastroenterol. - 2008; 42: 128-33.

[35] Thomopoulos K.C., Vagenas K.A., Vagianos C.E. et al. Changes in aetiology and clinical outcome of acute upper gastrointestinal bleeding during the last 15 years // Eur. J. Gastroenterol. Hepatol. -2004. -Vol. 16. -P. 177-182.

[36] Toh C.H., Hoots W.R. The scoring system of the Scientific and Standardization Committee on disseminated intravascular coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. J Thromb Haemost. 2007;5(3):604-606.

[37] Uemera N., Sugano., Hiraishi H, et al. Risk factor profiles, drug usage. And prevalence of aspirin-associated gastroduodenal inyurens among high-risk cardiovascular Japanese patients: The results from the MAGIC study. // J. Gastroenterolgy. 2014. № 49. Рю.14-24.

[38] Van Leerdam M.E., Vreeburg E.M., Rauws E.A. et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000 // Am. J. Gastroenterol. -2003. -Vol. 98. -P. 1494-1499.