



## The mechanism of combination with hemocoagulase and pantoprazole in upper gastrointestinal bleeding

Ming-Ke Yan<sup>1</sup>, Lei Bao<sup>1✉</sup>, Ying-Xing Wang<sup>1</sup>, Xiao-Hua Xia<sup>1</sup>, Qing-Hua Wang<sup>2</sup>

<sup>1</sup>Emergency Department, Kunshan NO.1 Peoples Hospital, Kunshan 215300, China

<sup>2</sup>Digestive department, Kunshan NO.1 Peoples Hospital, Kunshan 215300, China

### ARTICLE INFO

#### Article history:

Received 7 Jul 2016

Received in revised form 17 Jul 2016

Accepted 12 Jul 2016

Available online 24 Jul 2016

#### Keywords:

Upper gastrointestinal bleeding

Hemocoagulase

Pantoprazole

Mechanism.

### ABSTRACT

**Objective:** Through the combination with hemocoagulase and pantoprazole on gastrointestinal bleeding, to observe the changes of serum BUN (blood urea nitrogen), LPO (LPO), NO (nitric oxide), TNF- $\alpha$ (TNF alpha), hs-CRP (high sensitivity C reactive protein) and cortisol levels, and to explore the mechanism of combination. **Methods:** 110 cases of upper gastrointestinal bleeding in our hospital from January 2015 to September 2016 were selected and divided into the control group and the observation group, 55 cases for each group. Patients were treated with bed rest, fasting, intravenous nutrition, oxygen, and according to the individual situation actively supplement blood capacity, and the control group were treated with 40 mg intravenous pantoprazole treatment, 2 times/d; the patients in the observation group were treated with 2 kU hemocoagulase injection based on the treatment of control group, 2 times of intravenous injection per day, and all patients were treated for 3 d, and then the BUN, LPO, NO, TNF- $\alpha$ , hs-CRP and cortisol were detected. **Results:** (1) There were no significantly differences of the serum levels of BUN, LPO, and NO of the two groups before treatment ( $P>0.05$ ). After treatment, the serum levels the two groups were significantly lower than before treatment, and LPO, BUN, and NO levels in the observation group were significantly better than the control group ( $P<0.05$ ); (2) There were no significantly differences of the serum levels of TNF- $\alpha$ , hs-CRP, and cortisol of the two groups before treatment ( $P>0.05$ ). After treatment, the serum levels in the two groups were significantly lower than before treatment, and TNF- $\alpha$ , hs-CRP, and cortisol levels in the observation group were significantly better than the control group ( $P<0.05$ ). **Conclusions:** The treatment of patients with combined use of hemocoagulase and pantoprazole on gastrointestinal bleeding, can significantly improve the serum levels of BUN, LPO, NO, TNF- $\alpha$ , hs-CRP and cortisol levels, and further illustrates the synergistic effect of the combination, also shows that the combination of two drugs for patients with upper gastrointestinal bleeding can improve the symptoms of hemorrhage, reduce inflammation and stress, and improve the treatment effect.

## 1. Introduction

Upper gastrointestinal is the upper part of the digestive tract of the flexor ligament, upper gastrointestinal bleeding is a common clinical disease, refers to the esophagus, stomach, duodenum or pancreatic bile and other parts of the bleeding caused by pathological changes, and its manifested symptoms is hematemesis or melena in clinic. Most of the acute peripheral circulatory failure caused by the

decrease of blood volume, which has the characteristics of high incidence, high mortality, complicated etiology, such as peptic ulcer, acute gastric mucosal injury, esophageal gastric varices, gastric cancer and so on. For the treatment of upper gastrointestinal hemorrhage, to ensure hemostasis, blood volume, timely and effective hemostasis can not only control the disease and prevent further development, but also alleviate the effect of patients with clinical symptoms and signs, improve the prognosis, and it has a role in promoting the life quality of the patient protection<sup>[1,2]</sup>. This study aimed to observe the changes of serum BUN, LPO, NO, TNF- $\alpha$ , hs-CRP and cortisol levels by methods of the combination with hemocoagulase and pantoprazole in upper gastrointestinal bleeding, and to explore the mechanism of this combination.

✉Corresponding author: Lei Bao, Emergency Department, Kunshan NO.1 Peoples Hospital, Kunshan 215300, China.

Fund Project: Health Department of Jiangsu Province (project number: JD201599).

## 2. Materials and methods

### 2.1. General information

110 cases of upper gastrointestinal bleeding in our hospital from January 2015 to September 2016 were selected and divided into the control group and the observation group. There were 55 patients in the control group, including 30 male cases and 25 female cases; aged 25–65; etiology: 19 cases of gastric ulcer bleeding, 15 cases of duodenal ulcer bleeding, 11 cases of erosive gastritis bleeding, 5 cases of esophageal variceal bleeding, 5 cases of compound ulcer bleeding. There were 55 patients in the observation group, including 31 male cases and 24 female cases; aged 24–69; etiology: 20 cases of gastric ulcer bleeding, 13 cases of duodenal ulcer bleeding, 12 cases of erosive gastritis bleeding, 4 cases of esophageal variceal bleeding, 6 cases of compound ulcer bleeding. The general data of the two groups were analyzed by statistical comparison method, and the results showed no significant difference ( $P>0.05$ ).

### 2.2. Case inclusion criteria

(1) the clinical examination of upper digestive tract hemorrhage with diagnostic criteria; (2) to use the drug in the treatment was well tolerated and no taboo; (3) agree with this intention and treatment and signed informed consent.

### 2.3. Case exclusion criteria

(1) the important organs such as heart, liver and kidney function and other serious damage; (2) recently taking other drugs may affect the results; (3) the treatment process to replace or add drugs; (4) lactating and pregnant women.

### 2.4. Method

Patients were treated with bed rest, fasting, intravenous nutrition, oxygen, and according to the individual situation actively supplement blood capacity, and the control group were treated with 40 mg intravenous pantoprazole treatment, 2 times/d; the patients in the observation group were treated with 2 kU hemocoagulase injection based on the treatment of control group, 2 times of intravenous

injection per day, and all patients were treated for 3 d.

### 2.5. Observation index

After treatment in the morning fasting venous blood samples, and then the BUN (blood urea nitrogen), LPO (LPO), NO (nitric oxide), TNF- $\alpha$  (TNF alpha), hs-CRP (high sensitivity C reactive protein) and cortisol were detected.

### 2.6. Statistical analysis

We used SPSS17.0 software package to process the test result data, mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ) represents measurement data, the use of  $t$  test was to compare the difference between groups, and count data between groups was expressed by using the method of  $\chi^2$ ; with  $P<0.05$  as a statistically significant.

## 3. Results

### 3.1. The level of LPO, BUN and NO

Before treatment, there was no significant difference in the levels of serum LPO, BUN, and NO between the control group and observation group ( $P>0.05$ ). Compared with the same group before treatment, the difference in the levels of serum LPO, BUN, and NO was significant ( $P<0.05$ ), and the observation group were significantly better than the control group. LPO, BUN, and NO levels were significantly better than the control group ( $P<0.05$ ) (Table 1).

### 3.2. The level of TNF- $\alpha$ , hs-CRP and cortisol

Before treatment, there was no significant difference in the levels of TNF- $\alpha$ , hs-CRP, and cortisol between the two groups ( $P>0.05$ ); Compared with the same group before treatment, the difference in the levels of TNF- $\alpha$ , hs-CRP, and cortisol was significant ( $P<0.05$ ), and the observation group were significantly better than the control group. TNF- $\alpha$ , hs-CRP, and cortisol levels were significantly better than the control group ( $P<0.05$ ) (Table 2).

**Table 1**

Comparison of LPO, BUN, and NO before and after treatment in two groups ( $n=55, \bar{x}\pm s$ ).

Group	Time	BUN (mmol/L)	LPO (nmol/L)	NO ( $\mu$ mol/L)
Control group	Before treatment	11.01 $\pm$ 5.76	9.78 $\pm$ 4.15	68.65 $\pm$ 18.53
	After treatment	7.26 $\pm$ 2.34*	7.92 $\pm$ 3.27*	76.17 $\pm$ 18.14*
Observation group	Before treatment	10.88 $\pm$ 4.76	9.41 $\pm$ 4.52	69.06 $\pm$ 21.50
	After treatment	5.75 $\pm$ 1.18#	6.63 $\pm$ 3.12#	82.84 $\pm$ 19.53#

Compared with before treatment, \* $P<0.05$ ; compared with the control group, # $P<0.05$ .

**Table 2**

Comparison of TNF- $\alpha$ , hs-CRP, and cortisol before and after treatment in two groups ( $n=55, \bar{x}\pm s$ ).

Group	Time	TNF- $\alpha$ (ng/L)	hs-CRP ( $\mu$ g/L)	Cortisol ( $\mu$ g/L)
Control group	Before treatment	12.13 $\pm$ 3.14	18.01 $\pm$ 5.23	362.36 $\pm$ 36.71
	After treatment	8.52 $\pm$ 1.15*	12.88 $\pm$ 3.74*	340.23 $\pm$ 20.42*
Observation group	Before treatment	12.65 $\pm$ 3.01	17.92 $\pm$ 4.99	361.85 $\pm$ 37.59
	After treatment	5.72 $\pm$ 0.94#	6.28 $\pm$ 1.35#	312.57 $\pm$ 15.68#

Compared with before treatment, \* $P<0.05$ ; compared with the control group, # $P<0.05$ .

#### 4. Discussion

Upper gastrointestinal bleeding is including pancreatic or bile duct, the ligament of Treitz above digestive tract disease caused by bleeding, its etiology is various, diagnosis of endoscopic examination as the gold index, but for patients with severe acute illness, not suitable for endoscopic examination, should be based on clinical manifestations such as hematemesis, melena and hemorrhagic peripheral circulatory failure manifestations, laboratory examination and combining with the history and hemoglobin level judgment[3,4]. Patients with severe upper gastrointestinal bleeding, can cause hemorrhagic shock, causing serious threat to the lives of patients and patients with upper digestive tract hemorrhage after digestion in the stomach will not only aggravate the bleeding site condition, and will directly affect the coagulation function, platelet inhibition of gastric acid, therefore, timely control of hemorrhage and effective secretion is the main treatment method[5].

Hemocoagulase Agkistrodon in Changbai Mountain was extracted from freeze-dried venom and refined, which mainly contains thrombin and thrombin like enzyme induced, can release a series of coagulation factors, has prompted the prothrombin activation, accelerate thrombin formation, thereby stimulating platelet aggregation and accelerating the coagulation process. The hemostatic function rapidly onsets after intravenous administration of 10 min to work. In addition, hemocoagulase only plays a role in thrombin like normal blood vessels, do not play a thromboplastin like effect, does not cause platelet in normal vascular adhesion, therefore, play a role at the same time will not induce coagulation thrombosis[6,7]. Pantoprazole is a proton pump inhibitor, can inhibit gastric acid secretion, thereby reducing the acidic microenvironment, the gastric pH increased, and blood in the alkaline environment will achieve rapid solidification, reduce bleeding, promote blood coagulation. Research shows that when the pH value of gastric juice reached above 4 after the dissolution of coagulation induced loss of pepsin, shorten the coagulation time, pantoprazole strong crack acidinhibitor, will maintain the level of pH in patients with bleeding, conducive to platelet aggregation, make blood clot dissolved, to quickly and completely hemostatic effect[8,9]. With the combination of the two drugs, to promote each other, and complement each other can achieve high efficiency (effect) and available (short effective time), security (targeting obvious), convenience (administration frequency, multi way) of the hemostatic effect[10].

BUN is a human protein metabolism in the liver of the end product, is the main component of non-protein nitrogen in the circulation to the kidneys excreted into the urine, the concentration change will affect the content of non-protein nitrogen in a larger extent, clinical detection, detection of BUN are often used to replace the non-protein nitrogen. BUN is an important index of upper gastrointestinal bleeding. It is closely related with upper gastrointestinal bleeding. The change of the level of the upper gastrointestinal bleeding is very important for correct judgment of upper gastrointestinal bleeding. BUN is elevated in patients with gastrointestinal bleeding because of bleeding blood into the intestinal lumen, the intestinal tract of various proteolytic enzyme and peptide enzyme combination effect, decomposition of amino acids, followed by reduction of nitrogen radicals, generated after nitrogen absorbed into the blood, further synthesis of urea caused by the increase of BUN, coupled with digestion after bleeding

stress reaction increased, further promote the decomposition of protein and accelerate the synthesis of urea. In addition, after the occurrence of upper gastrointestinal bleeding, the function of each organ attenuation caused by BUN discharge reduction is also one of the reasons for the rise of BUN[11-13]. In this study, the serum level of BUN after treatment in two groups were significantly decreased compared with before treatment ( $P<0.05$ ), and using the combined use of hemocoagulase and pantoprazole in patients, the level of the degree of improvement is better, and the drug combination for the better control effect of bleeding can indirectly promote the recovery of the function of each organ of the body.

LPO is the oxygen free radical and poly unsaturated fatty acids formed by the reaction product of the peroxide content of LPO, the normal level is very low, but the body function damage or in pathological conditions, lipid peroxidation, induce the increase of LPO, the excess LPO can damage the biological membrane, structure and function of cells and cell membrane the cause further damage. Recent studies show that the upper gastrointestinal bleeding, oxygen free radicals increased significantly, while the patients with gastrointestinal mucosa ischemia and abnormal blood flow distribution, in this state, increased oxygen free radical level than the body's ability of scavenging oxygen free radicals, too much can further aggravate gastrointestinal mucosal injury[14,15]. The results in this study, patients with gastrointestinal bleeding using hemocoagulase combined with pantoprazole in the treatment of upper digestive, the level of LPO patients decreased significantly, and it was significantly higher than the simple use of pantoprazole in patients with combined medication that has a more significant free radical scavenging capacity, maintenance of tissue oxygen free radical scavenging function, prevent oxygen free radical aggregation *in vivo* tissue, to prevent tissue damage.

NO is L-arginine by NOS (NO synthase) produced NOS, divided into primary type (present in endothelial cells, nerve and smooth muscle cells, platelets) and inducible (found in macrophages, neutrophils, gastrointestinal mucosal cells). NO is a lipophilic substances that penetrate the cell membrane easily, thereby stimulating a series of biological reaction, when gastric acid, alcohol induced loss of substance invade the digestive tract, stimulate the release of NO, the blood vessels, inhibit platelet aggregation and adhesion to physiological protection. After the occurrence of gastric ulcer, the NO in the tissue has the function of maintaining the blood flow around the ulcer and promoting the healing of ulcer[16,17]. In this study, patients with gastrointestinal bleeding using hemocoagulase combined with pantoprazole in the treatment of upper digestive, NO levels of patients were significantly increased, the level is higher than that of the control group patients, and the combined medication is more beneficial to the body protective substances, promoting patients' symptoms and signs of improved to a greater extent. TNF- $\alpha$  is a kind of cytokine secreted by activated monocytes, which has many biological functions and is closely related to the occurrence and development of many diseases. The level of TNF- $\alpha$  is related to the degree of stress reaction caused by upper gastrointestinal bleeding. Under the stimulation of hemorrhage, the activation of monocyte macrophages increased, the secretion of TNF- $\alpha$  increased, and the level of TNF- $\alpha$  increased. As an inflammatory mediator, excessive increase of TNF- $\alpha$  can cause further damage to the body's tissues, which can inhibit the immune function of the body, which can lead to infection or organ failure. In the gastrointestinal tract, this can be manifested as hemorrhagic injury. For patients with upper

gastrointestinal bleeding, inflammatory reaction of TNF- $\alpha$  can participate in the ulcer department, further erosion of blood vessels, thereby increasing the development of hemorrhage, high levels of TNF- $\alpha$  will become a negative factor, hemostasis therefore, using a certain method to reduce the levels of TNF- $\alpha$ , helps to eliminate the treatment of bleeding[18,19]. In this study, patients with gastrointestinal bleeding using hemocoagulase combined with pantoprazole in the treatment of upper digestive, levels of TNF- $\alpha$  patients decreased significantly, and the level was significantly lower than the control group ( $P < 0.05$ ), indicating that inflammation combination therapy can improve the body's immunity, promote the body recovery and stress state of suppression, and improve TNF- $\alpha$  level, which has an important role to improve the overall therapeutic effect.

Hs-CRP is in the liver of a systemic inflammatory response to nonspecific marker synthesis, is commonly used in clinical indicators, the inflammatory reaction of the body has a certain value in monitoring, reports show that the stress on the body to produce bleeding may lead to abnormal immune status, promote hs-CRP and other inflammatory factors content increases. Systemic inflammatory reaction and further inhibit the immune function. Occurrence of upper gastrointestinal bleeding after stimulation of the liver synthesis of a large number of hs-CRP, and through the classical pathway of complement activation and consumption after the release of inflammatory mediators, to further promote the occurrence and development in the environment of inflammation[20]. Cortisol belongs to glucocorticoids, a stress hormone, with the metabolism of carbohydrate effect of adrenal cortical hormone, under normal circumstances, the body can secrete cortisol and content on the good control and regulation, the body needs to maintain the normal physiological function of cortisol, can control mood and health, immune cells and inflammation, maintenance the organization function. When the upper gastrointestinal bleeding occurs, the body is subjected to strong stimulation and stress response, rapid increase in cortisol levels, therefore, the cortisol content of the monitoring can reflect the body's stress state[21]. In this study, patients with gastrointestinal bleeding using hemocoagulase combined with pantoprazole in the treatment of upper digestive, hs-CRP and cortisol levels in patients decreased significantly, and the level was significantly lower than the control group ( $P < 0.05$ ), the combined medication by reducing hs-CRP and cortisol levels in patients, alleviate the stress response of the organism itself, reduce inflammatory reaction in the environment, which can promote the body to improve clinical symptoms and promote the recovery of immune patients.

In conclusion, the treatment of patients with combined use of hemocoagulase and pantoprazole on gastrointestinal bleeding, can significantly improve the serum levels of BUN, LPO, NO, TNF- $\alpha$ , hs-CRP and alpha cortisol levels, and further illustrates the synergistic effect of the combination, also shows that the combination of two drugs for patients with upper gastrointestinal bleeding can be improve the symptoms of hemorrhage, reduce inflammation and stress, and improve the treatment effect.

## References

- [1] Wang JY. Clinical observation on the treatment of acute upper gastrointestinal hemorrhage. *Med Theory Pract* 2013; **26**(11): 1456-1457.
- [2] Johann PH, Evangelos K, Sveinn G, et al. Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based setting. *Scan J Gastroenterol* 2013; **48**(4): 439-447.
- [3] Colin JC, Joe W, Timothy RC. Comorbidities affect risk of nonvariceal upper gastrointestinal bleeding. *Gastroenterology* 2013; **144**(7): 1384-1393.
- [4] Zhang MG. Diagnosis and treatment of upper gastrointestinal hemorrhage and its development. *Chinese Doc* 2012; **40**(6): 3-7.
- [5] Lin SF. Hemocoagulase and pantoprazole used in clinical observation on upper gastrointestinal hemorrhage. *Chin J Pract Med* 2016; **11**(7): 133-134.
- [6] Sheng YW, Yuan CH, Yan QZ, et al. Hemocoagulase atrox reduces vascular modeling in rabbit carotid artery adventitia. *Int J Clin Exp Pathol* 2013; **6**(11): 2386-2395.
- [7] Deng XF, Wang YM, Zou GX. Pantoprazole combined with Hemocoagulase For Injection in treatment of upper gastrointestinal hemorrhage the clinical curative effect of. *Clin Rational Use Drugs* 2016; **9**(4C): 49-50.
- [8] Wang CZ. Pantoprazole in the treatment of upper digestive tract hemorrhage curative effect observation of. *Jilin Med J* 2013; **34** (8): 1472.
- [9] Ji JY. OBServation of the medical forum tract hemorrhage curative effect of pantoprazole in the treatment of upper digestive. *Med Forum* 2015; **19**(36): 5078-5079.
- [10] Bai L. Hemocoagulase and pantoprazole used in clinical evaluation of upper gastrointestinal bleeding. *Chin Pract Med* 2016; **11**(24): 120-121.
- [11] Qiu WW, Chen JR. Clinical analysis of changes of urea nitrogen in the course of acute upper gastrointestinal bleeding. *J Chin Med* 2015; **50**(8): 84-86.
- [12] Chen J, Wang XJ, Zhu FX, et al. Serum urea nitrogen and fecal occult blood test in the diagnosis of upper gastrointestinal bleeding. *J Pract Med* 2015; **22**(1): 75-76.
- [13] Minoru T, Fuminobu S, Rumiko H, et al. Patient characteristics with high or low blood urea nitrogen in upper gastrointestinal bleeding. *World J Gastroenterol* 2015; **21**(24): 7500-7505.
- [14] Rudolf J, Schaur, Werner S, et al. 4-hydroxy-nonenal-a bioactive lipid peroxidation product. *Biomolecules* 2015; **5**(4): 2247-2337.
- [15] Plamena R, Angelova, Mathew H, et al. Lipid peroxidation is essential for  $\alpha$  synuclein induced cell death. *J Neurochem* 2015; **133**(4): 582-589.
- [16] Katarzyna A, Broniowska, Bryndon J, et al. How the location of superoxide generation influences the  $\beta$ -cell response to nitric oxide. *J Biol Chem* 2015; **290**(12): 7952-7960.
- [17] Jing D, Man LL, Dong DK, et al. Nitric oxide induces cotyledon senescence involving co-operation of the NES1/MAD1 and EIN2-associated ORE1 signalling pathways in Arabidopsis. *J Exp Bot* 2014; **65**(14): 4051-4063.
- [18] Cheng J. Clinical evaluation of serum IL-6, TNF- $\alpha$  and TGF-beta 1 in patients with gastric ulcer. *J Radio Immunol* 2012; **25**(4): 399-401.
- [19] Du Y, Zhao WC, Lu LL, et al. Study on the antiulcer effects of *Veronicastrum axillare* on gastric ulcer in rats induced by ethanol based on tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and endothelin-1 (ET-1). *Asian Pac J Trop Biomed* 2013; **3**(12): 925-930.
- [20] Tomizawa M, Shinozaki F, Hasegawa R, et al. Reduced hemoglobin and increased C-reactive protein are associated with uppergastrointestinal bleeding. *World J Gastroenterol* 2014; **20**(5): 1311-1317.
- [21] He JW, Xia XL, Wang CQ. Effects of triple therapy on acute upper gastrointestinal bleeding and its effect on the sensitivity of C reactive protein and cortisol. *Med Theory Pract* 2014; **27**(1): 57-58.