Research Paper

Clinical Efficacy, Safety and Impact of Octreotide Combined with Pantoprazole in the Treatment of Gastrointestinal Bleeding

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This study analyzed the clinical efficacy, safety and effect on coagulation function of octreotide combined with pantoprazole in the treatment of gastrointestinal bleeding. Analysis was conducted using 82 individuals with gastrointestinal bleeding who were treated in Hangzhou Ninth People's Hospital from June 2021 to June 2023. They were divided into a single group and combination group according to the actual medication plan. The medication regimen of the single group is pantoprazole, and the medication regimen of the combination group is combination of octreotide and pantoprazole, where the medication cycle is 7 d. The medication effects, inflammatory factor indicators, adverse drug reactions, and coagulation function of the two groups of patients were observed. After treatment, the total effective rate of treatment in the single group was 87.8 %, while in the combined group was found to be 100 % ($p<0.05$). After medication, the inflammatory factor indicators in both groups were lower than before medication, and even lower in the combination group ($p<0.05$). During the medication, the incidence of adverse drug reactions in the single group was 7.32 % and in the combination group was 9.76 % ($p>0.05$). The coagulation function indicators of the latter two groups improved and the combination group was showed better results ($p<0.05$). For gastrointestinal bleeding, the medication regimen of octreotide+pantoprazole is effective, helps to reduce the patient's inflammation level and improve the coagulation function.

Key words: Octreotide, pantoprazole, gastrointestinal bleeding, coagulation, somatostatin receptor

Gastrointestinal Bleeding (GB) is a relatively common digestive system disease that develops rapidly and may cause serious hazards such as anemia, shock, ulcers, rebleeding complications, and even death. Its clinical features mainly include hematemesis, hematochezia, melena, abdominal pain, dizziness, fatigue and decreased blood pressure. Therefore, GB should receive prompt attention and medical treatment to reduce the occurrence of complications, and improve the treatment effect. The treatment method for GB is mainly symptomatic treatment according to its cause, location and severity of bleeding. The more common methods include drug treatment, endoscopic treatment, surgical treatment, vascular interventional treatment and drug treatment of underlying diseases, etc.[1]. Drug treatments are mainly divided into hemostatic drug usage, gastric acid inhibitors, prokinetic drugs, antibiotics, vasoactive drugs and antiviral drugs, etc. Currently, octreotide and pantoprazole are the main drugs for the treatment of GB. Among them, octreotide is a prokinetic drug that activates Somatostatin Receptor (SSTR) in the gastrointestinal neurosecretory system to shrink the intestines and increase the gastrointestinal motility, thereby reducing the risk of GB[2]. Pantoprazole belongs to the class of gastric acid inhibitors and more specifically it is a proton pump inhibitor. Pantoprazole can treat GB by inhibiting the proton pump in gastric mucosal cells and reducing gastric acid secretion. Moreover, pantoprazole can also effectively prevent the occurrence of gastrointestinal ulcers[3]. This study aims to study the drugs for the treatment of GB in order to provide valuable reference for clinical medication.

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MATERIALS AND METHODS

General information:

82 GB individuals who visited Hangzhou Ninth People's Hospital from June 2021 to June 2023 were selected as based on the inclusion and exclusion criteria, and were divided into a single group (n=41) and the combined group (n=41).

Inclusion criteria:

Patients with gastroscopy; patients who met the diagnostic criteria for GB; patients no allergic reaction to proton pump inhibitors and gastrointestinal prokinetic drugs and patients with good compliance towards the medication regimen octreotide pantoprazole were included in this study.

Exclusion criteria:

Patients with other serious blood diseases; patients having severe genetic diseases; patients with serious diseases such as heart and liver and patients whose clinical data was incomplete were excluded from the study.

Treatment method:

Single group: The medication regimen included was pantoprazole. Pantoprazole sodium for injection is produced by Zhejiang Huarun Shuanghe Pharmaceutical Co., Ltd., whose specification was 40 mg/bottle, with the national drug approval number, H20073730. Intravenous infusion of 40 mg was given 2 times/d. Before injection, 10 ml of 0.9 % sodium chloride injection was injected into the freeze-dried powder vial which was dissolved into 100 ml of 0.9% sodium chloride injection for intravenous infusion; the drip was finished within 60 min. It must be used up within 4 h after dissolving and diluting. It was instructed not to use other solvents or other drugs to dissolve or dilute the drug and this medication course lasted for 7 d.

Compound group: Similarly, the medication regimen given for the combined group involved the combination of octreotide and pantoprazole. Octreotide acetate injection produced by Sinopharm Yixin Pharmaceutical Co., Ltd., whose specification is 1 ml:0.15 mg, with Sinopharm approval number, H20041558. Intravenous drip was given 2 times/d by adding 100 ml of 0.9 % sodium chloride injection to 0.1 mg of octreotide where the drip was finished within 60 min; the medication course lasted for 7 d.

Observation indicators:

Clinical medication effects: The clinical medication effect observation indicators are based on clinical characteristics such as bleeding, vomiting blood and melena. It was considered markedly effective if the above mentioned symptoms in patients disappeared within 2 d after taking the medication. Similarly, if these symptoms disappeared within 3 d after drug administration, then it was considered to be effective. If the patient's clinical symptoms did not improve or if bleeding re-occured after 3 d of medication, it was considered ineffective.

Total efficiency=apparent efficiency+effective efficiency

Inflammatory factors: Blood from the patients was collected venously to detect the patient's Interleukin-6 (IL-6), high-sensitivity C-Reactive Protein (hs-CRP) and Tumor Necrosis Factor-Alpha (TNF-α) values. Inflammation was directly related with the levels of these inflammatory factors which mean that lower the factors, lower is the inflammation.

Incidence of adverse drug reactions: The main adverse drug reactions of octreotide and pantoprazole are nausea, vomiting, diarrhea, abdominal pain, abnormal blood sugar and liver function, and dizziness and headache. The incidence of these adverse reactions in patients during medication were observed and recorded.

Coagulation function: Blood from the patient was collected to detect serum Fibrinogen (FIB), Activated Partial Thrombin Time (APTT), Thrombin Time (TT) and Prothrombin Time (PT). FIB helps to coagulate blood and stop bleeding, so higher level of FIB denotes better for gastrointestinal bleeding. Higher APTT represents delay in coagulation function, which means abnormal coagulation function or weak coagulation function, which easily increases the risk of bleeding; thus, lower APTT is better during gastrointestinal bleeding. Higher TT takes longer time for blood coagulation and slower coagulation speed of blood is not conducive to hemostasis. Therefore, lower TT is better during gastrointestinal bleeding. Higher PT means that the coagulation function is affected, coagulation time is prolonged and the blood clotting speed is slow. Therefore, during gastrointestinal bleeding, lower PT is better and is beneficial to the operation of coagulation function resulting to reduce the risk of bleeding.

Data analysis:

The data collected in the study was processed by Statistical Package of Social Sciences (SPSS) version 22.00 professional software and expressed as mean±deviation (x±s) using t-test or Chi-square (χ^2) test where $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The baseline data between the two groups was compared and there was no significant difference in the basic information ($p>0.05$) (Table 1).

Clinical effects of drugs between the two groups were compared. The total clinical effectiveness of the single group was found to be 87.8 % and that of the combination group was 100 % (Table 2).

Inflammatory factors such as Il-6, hs-CRP and TNF-α of the two groups were analyzed comparatively before and after medication (Table 3).

Incidence of adverse drug reactions between the two groups was evaluated. There were 3 patients with adverse drug reactions in the single group while 4 patients in the combination group (Table 4).

Similarly, the coagulation function indicators like FIB, APTT, TT and PT between the two groups of patients before and after medication were compared (Table 5).

TABLE 1: COMPARISON OF GENERAL INFORMATION BETWEEN THE TWO GROUPS (x±s)

Group	n	Gender (male/female)	Age (y)	Course of disease (d)	Bleeding volume (ml)
Single group	41	24/17	46.32±3.18	4.66±0.33	382.26±22.41
Combination group	41	23/18	46.51±3.22	4.67±0.32	386.24±23.18
t		0.025	0.023	0.018	0.024
p		0.917	0.936	0.964	0.921

TABLE 2: COMPARISON OF CLINICAL EFFECTS OF TWO GROUPS OF DRUGS (n, %)

Group	n	Effective	Efficient	Invalid	Total efficiency
Single group	41	19 (46.34)	17 (41.46)	5 (12.2)	36 (87.8)
Combination group	41	28 (68.29)	13 (31.71)	0	41 (100)
χ^2					7.289
p					0.001

TABLE 3: COMPARISON OF LEVEL OF INFLAMMATORY FACTORS (x±s) IN TWO GROUPS

Group	n	IL-6 (pg/ml)		hs-CRP (mg/ml)		TNF-α (μg/ml)	
		Before medication	After medication	Before medication	After medication	Before medication	After medication
Single group	41	36.72±3.56	18.84±2.96	43.18±4.18	26.35±2.18	3.62±0.58	1.91±0.43
Combination group	41	37.12±3.66	12.18±2.14	42.92±4.16	17.12±2.25	3.61±0.57	1.24±0.36
t		0.032	2.247	0.028	2.108	0.012	2.592
p		0.872	0.001	0.908	0.001	0.988	0.001

TABLE 4: COMPARISON OF INCIDENCE RATE OF ADVERSE DRUG REACTIONS (n, x±s)

Group	n	Discomfort and vomiting	Diarrhea and abdominal pain	Abnormal blood sugar	Abnormal liver function	Dizziness and headache	Overall incidence
Single group	41	1	1	0	0	1	7.32 %
Combination group	41	2	1	0	0	1	9.76 %
χ^2							0.562
p							0.223

TABLE 5: COMPARISON OF COAGULATION FUNCTION BEFORE AND AFTER MEDICATION (x±s)

Group	n	FIB (g/l)		APTT (s)		TT (s)		PT (s)	
		Before medication	After medication	Before medication	After medication	Before medication	After medication	Before medication	After medication
Single group	41	2.74±0.39	2.91±0.41	33.28±2.82	29.51±2.63	20.16±1.98	17.23±1.66	15.57±2.25	13.02±1.32
Combination group	41	2.75±0.39	3.42±0.44	33.44±2.69	26.18±2.36	20.34±2.01	14.52±1.55	15.48±2.23	11.32±1.14
t		0.027	1.026	0.03	1.192	0.029	0.996	0.028	1.126
p		0.935	0.001	0.923	0.001	0.927	0.001	0.931	0.001

GB is blood extravasation due to rupture of the mucosa or blood vessels in the gastrointestinal tract. Its pathological manifestations include mucosal erosion, ulcers, vasodilation, inflammatory cell infiltration and other changes. GB may cause abnormalities in coagulation function, such as changes in PT, APTT, FIB and other indicators. Assessing these indicators can help to assess the cause of bleeding and detect bleeding risk. Upper Gastrointestinal Bleeding (UGB) may also cause an inflammatory response. Monitoring inflammatory indicators can help to assess the degree of inflammation and the risk of infection. Some studies have shown that in GB patients, abnormal coagulation function may be related to the severity of bleeding and prognosis[4]. The reason is that prolonged PT and low platelet count can indicate an increased risk of bleeding and timely correction of coagulation abnormalities can help to reduce the risk of bleeding and improve prognosis. In addition, inflammatory response plays an important role in the process of GB, for example, TNF-α and IL-6 are often elevated. A study showed that the degree of inflammatory response is often closely related to the risk of infection, severity of illness and prognosis[5]. Therefore, monitoring inflammatory factor indicators can help to evaluate the patient's condition and guide medication.

One study pointed out that common adverse reactions when octreotide is used to treat GB include mild symptoms such as headache, nausea, diarrhea, abnormal blood sugar and serious adverse drug reactions rarely occur in medication practice; so it is widely used in clinical medication[6]. Studies have shown that when pantoprazole is used for GB medication, the adverse reactions caused by it are mainly mild discomfort symptoms such as headache, nausea, diarrhea, rash, fatigue, etc., which are acceptable[7]. In this study, the adverse reactions of the single group of drugs were lower than those of the combination group. However, there was little difference in the adverse drug reactions between the two groups. Therefore, whether it is a single drug or a combination of drugs, the safety of the two groups of drug regimens is relatively high.

Pharmacological principles of octreotide and pantoprazole in the treatment of GB were studied. Octreotide is a synthetic drug similar to growth hormone-releasing hormone, which relies on the release of growth hormone and acts on the anterior pituitary gland. It also exerts its effects by directly acting on the synthesis and secretion of insulin-like growth factors. In GB, the patient's mucosa will be damaged and resulting in the formation of ulcers very often. Octreotide can promote the proliferation and repair of gastrointestinal mucosal cells and can accelerate the healing of ulcers, so as to reduce bleeding and reduce inflammatory reactions[8]. In addition, octreotide can also promote the contraction of vascular endothelial cells, which can reduce the permeability of blood vessels and reduce the degree and risk of bleeding. Octreotide can also inhibit gastric acid secretion, thus reducing gastric mucosal damage and GB. Urai *et al.*[9], have pointed out that the therapeutic effect of octreotide is mainly to promote the release of growth hormone, thereby promoting tissue growth and repair. Similarly, Hu *et al.*[10], have pointed out that octreotide can inhibit gastric acid secretion and reduce gastric mucosal irritation and damage, thereby reducing the risk of GB. In this study, octreotide was added to the combination group, and the clinical effect was significantly better than that of single medication, indicating that octreotide plays a crucial role.

Pantoprazole is a proton pump inhibitor, and its main reason for treating GB is to inhibit gastric acid secretion. The main cause of GB is that the mucosa of the digestive tract is stimulated and damaged by gastric acid and other digestive juices, which leads

to ulcers, rupture and bleeding. Pantoprazole can specifically inhibit Hydrogen Potassium Adenosine Triphosphatase (H^+/K^+-ATPase) on the gastric mucosa, thus achieving the purpose of blocking gastric acid secretion and reducing gastric acidity. The gastric mucosa is less irritated and damaged, which reduces the risk of bleeding. As per the study and results of Bixia *et al.*[11], the clinical efficacy and safety of pantoprazole in the treatment of GB were recognized. This study suggests that pantoprazole can control gastric acid secretion and promote ulcer healing, thereby reducing the risk of GB. This study concluded that pantoprazole is an effective drug for the treatment of GB. In this study, the overall effect of pantoprazole medication regimen for a single group of patients was better, indicating that pantoprazole drug is more effective.

Further, we found that octreotide and pantoprazole reduces the inflammatory response. In the treatment of GB, octreotide relies on acting on the central and peripheral nervous systems to regulate the activity of immune cells, slow down the release of inflammatory mediators, and thereby reduce the occurrence of inflammatory reactions. In addition, octreotide can also promote cell growth and proliferation, promote the growth of gastrointestinal mucosal cells, promote the healing and repair process of ulcer surfaces, and slow down or stop the inflammatory response. One study found that when octreotide was used to treat GB, inflammatory indicators were significantly reduced, indicating that octreotide can effectively reduce the occurrence of inflammatory reactions[12]. Another study found that octreotide can reduce the occurrence of inflammatory reactions by reducing the release of inflammatory mediators, and promote the healing of ulcers, which is beneficial to the treatment of GB[13]. In this study, after adding octreotide to the combination group, the indicators of inflammatory factors in patients were significantly reduced, which is consistent with the conclusions of other studies.

Pantoprazole relies on proton pump inhibition to reduce gastric acid secretion. Its main principle is to reduce gastric acid secretion by inhibiting H^+/K^+-ATPase on the gastric wall, thereby reducing the acidity of gastric juice and protecting the gastric mucosa from or lower suffer corrosion and irritation, thus reducing the occurrence of inflammatory reactions. In addition, pantoprazole can also increase the blood flow of the gastric mucosa, which can promote the repair and regeneration of gastric mucosal epithelial cells, thereby accelerating the healing process of the ulcer surface to achieve the purpose of reducing the inflammatory reaction. One study pointed out that pantoprazole can significantly reduce the release of inflammatory mediators in the treatment of GB to reduce the process of inflammatory response, thereby promoting the healing of ulcers and alleviating bleeding symptoms[14]. In this study, both groups of patients used pantoprazole, and the inflammatory factor indexes of both groups of patients were reduced after taking the medication. This result is consistent with the conclusions of other studies.

It was found that octreotide and pantoprazole can improve coagulation function. Octreotide relies on activating SSTR to inhibit gastric acid secretion and promote gastric mucosal repair. The activation of SSTR can rely on a variety of signaling pathways, which can inhibit adenylyl cyclase and increase intracellular cyclic guanosine monophosphate levels to achieve physiological processes such as preventing gastric acid secretion and promoting cell proliferation and apoptosis. octreotide promotes the aggregation and adhesion of platelets, thereby enhancing the role of platelets at the bleeding site, thereby achieving the purpose of thrombosis and hemostasis. In addition, octreotide can promote the conversion of prothrombin into thrombin, thus accelerating the blood coagulation process and promoting wound healing and hemostasis. One study pointed out that in GB treatment, the recovery of coagulation function is closely related to the prognosis. Patients with faster recovery of coagulation function tend to have lower bleeding risks and faster recovery[15]. Therefore, improving the patient's coagulation function is one of the keys to treating gastrointestinal bleeding. This study attached great importance to the patients' coagulation function indicators, and the coagulation function indicators of both groups of patients were improved after taking the medication.

As a proton pump inhibitor, pantoprazole's main function is to reduce the patient's gastric acid secretion to reduce the irritation of gastric acid to the patient's ulcer. Pantoprazole itself does not directly affect the patient's coagulation function, but its inhibitory effect on gastric acid secretion can directly affect ulcer healing and coagulation function. Because it reduces gastric acid stimulation and promotes ulcer healing, it reduces blood vessel exposure and reduces the impact of the ulcer site on coagulation factors, which indirectly helps to improve coagulation function.

In this study, whether single drug or combined drug was used, the clinical efficacy was high. However, the combined drug effect is better than monotherapy and it has a significant effect on reducing inflammatory reactions and improving patients' coagulation function. There are also some shortcomings in this study. For example, pantoprazole has the effect of reducing gastric acid secretion and the patient's gastric juice pH value was not monitored in this study. GB is closely related to gastrokinetic indicators, and this study did not detect the gastrokinetic indicators in patients. In future research, these aspects should be addressed.

Conflict of interests:

The authors declared no conflict of interests.

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