Research Paper

Study on the Effectiveness of Zhigancao Decoction as an Adjunct to Western Medicine in the Treatment of Upper Gastrointestinal Bleeding

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To research the effectiveness of Zhigancao decoction in treating upper gastrointestinal bleeding when used in conjunction with Western therapy. The two groups of 109 patients with upper gastrointestinal bleeding who were admitted to our hospital between January 2022 and January 2023 were compared with regard to the total effective rate of therapy, haemostatic impact, traditional Chinese medicine evidence score, blood rheological index and serum-related parameters. The research group (n=54, utilizing Zhigancao decoction in addition to Western medication) and the control group (n=55, receiving only Western medical treatment) were randomized into the two groups at random. The study group's total treatment efficacy rate was greater ($p<0.05$) compared to the control group. In comparison to the control group, the research group's hemostasis time, blood pressure stabilization time, and time to treat abdominal discomfort were all shorter ($p<0.05$). After treatment, the traditional Chinese medicine syndrome scores of the research group were lower than those of the control group ($p<0.05$). Following treatment, the research group's erythrocyte sedimentation rate was lower than that of the control group ($p<0.05$), and their levels of polycythemia vera, whole blood high cut viscosity, and whole blood low cut viscosity were all higher than those of the control group ($p<0.05$). Serum 6-keto-prostaglandin F1 alpha and malondialdehyde levels were lower ($p<0.05$), superoxide dismutase and prostaglandin E2 levels were lower ($p<0.05$) in the research group than in the control group following treatment. The treatment of upper gastrointestinal bleeding with Zhigancao decoction as an adjunct to Western medicine can further enhance the hemostatic effect and effectively improve the hemodynamic status. The down-regulation of prostaglandin E2 and 6-keto-prostaglandin F1 alpha levels as well as the body's reduced stress response may be part of the mechanism of action.

Key words: Upper gastrointestinal bleeding, Zhigancao decoction, stress response, blood rheology

Upper gastrointestinal hemorrhage is a common clinical emergency. It is a bleeding symptom caused by lesions of the stomach, esophagus, pancreatic duct, duodenum and bile duct above the ligament of Treitz, and is characterized by black stools and vomiting of blood[1]. Peripheral circulatory abnormalities may be caused if bleeding amounts exceed 20 % of the blood volume in circulation or 1000 ml in a brief amount of time. If untreated, the patient may experience catastrophic complications such hemorrhagic shock and hypoxia[2,3]. At the moment, medications that prevent gastric acid secretion are the primary clinical treatment for upper gastrointestinal bleeding, but the results are less satisfactory, the adverse effects are more serious, and the treatment takes longer and is more likely to be repeated.

The fusion of Chinese and Western medicine has substantially helped the treatment of upper gastrointestinal hemorrhage recently. The study by Yue *et al*.[4] and He *et al*.[5] is a typical study in this regard.

Upper gastrointestinal bleeding belongs to the category of "vomiting blood" and "blood in the stool" in Chinese medicine, and the main pathogenesis is the vicious heat that compels the blood to move, and the main treatment direction is to cool the blood and stop bleeding, dispel blood stasis and disperse the knots[6].

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A traditional Chinese medicine sage named Zhang Zhongjing is credited with creating the Zhigancao decoction, a treatment for "pulse disorders". It has been shown to be effective in the treatment of cardiac arrhythmias, lung cancer, pulmonary infections and persistent atrial fibrillation[7,8]. However, in upper gastrointestinal haemorrhage, it has been shown to be more effective in the treatment of the heart. However, the role in upper gastrointestinal bleeding has been reported in few studies. Patients with upper gastrointestinal bleeding may suffer from pallor, chest tightness, chest pain, palpitations, shortness of breath, weakness, sweating, aggravated by emotion and activity, and loose stools due to loss of schooling, which are typical indications of yin and Yang deficiency in Zhigancao decoction. We anticipate that Zhigancao decoction will produce better results in the treatment of upper gastrointestinal bleeding and offer a more reliable safety assurance when used in conjunction with Western medicine.

In order to provide a more helpful and reliable reference for the future clinical management of upper gastrointestinal bleeding; this study will assess the effectiveness of Zhigancao decoction as a complementary therapy to Western medicine in the treatment of upper gastrointestinal bleeding.

MATERIALS AND METHODS

Experimental preparation:

We randomly divided 109 patients with upper gastrointestinal hemorrhage admitted to our hospital between January 2022 and January 2023 into two groups; the research group (n=54), which received Zhigancao decoction in addition to Western medicine, and the control group (n=55, which received only Western medicine). The medical ethics committee of our university approved the informed consent form, which was filled out and signed by all research participants.

Inclusion and exclusion criteria:

Inclusion criteria: All patients met the diagnostic criteria for upper gastrointestinal bleeding in internal medicine and practical Chinese internal medicine and were diagnosed by gastroscopy[9,10]; the onset time was (12-48) h; and they received complete treatment in our hospital after the onset. **Exclusion criteria:** Severe cardiac, hepatic or renal dysfunction; other bleeding diseases; psychiatric disorders; immunological disorders; patients who were pregnant or nursing, and patients who had an allergy to any of the study medicines were excluded.

Methods:

Patients in both groups were immediately admitted to hospital, fasted, promptly replenished with blood, anti-infection and corrected water-electrolyte disturbances. Symptomatic supportive treatment was given according to clinical symptoms and intensive nutritional support. Monitor vital signs and give blood transfusion promptly when patients experience syncope or drop in blood pressure or hematocrit <25.0 % when changing position.

The control group's patients received Western medicine. Omeprazole injection (Jiangsu Oxycon Pharmaceutical Co., Ltd., approval number: State Drug Administration H20059053, specification 40 mg) 40 mg plus 0.9 % sodium chloride injection 100 ml intravenous drip, each drip time (20-30) min, 1 time/d for 7 d.

The research group in the study received the addition of Zhigancao decoction. 90 g of raw Dihuang; 30 g each of roasted licorice, Maitong and aconite beads; 15 g each of radix *Codonopsis pilosulae*, Fritillariae and jujube; 10 g each of dried ginger and cinnamon sticks were decocted in water, thickened and 50 ml of juice was extracted and taken in two doses. Use 3 doses continuously.

Efficacy assessment:

Referring to the diagnostic criteria and treatment protocol for upper gastrointestinal bleeding, successful hemostasis within 24 h of onset, normal hemoglobin and stable blood pressure was considered as effective. Successful hemostasis within (24-72) h of onset, hemoglobin and blood pressure do not continue to fall was considered as moderate; failure to achieve the above targets or even worsening was considered as ineffective.

Total effective rate of treatment=(Number of significant instances+Number of effective cases)/ Number of cases×100 %

Observed indicators:

The time of haemostasis, time of blood pressure stabilization and time of abdominal pain relief were recorded. Before and after treatment, the "Diagnostic and Curative Criteria for Chinese Medicine Evidence" were used to evaluate the Chinese medicine symptoms[11], which included the eight items of gastric fullness, mental fatigue and

weakness, burning heat in the stomach, dry stools, bitter mouth and dry throat, yellow and red urine, acidity and belching, thirst and cold drinks, and blood in the stool, with 0 points for no symptoms, mild means 0-3 points; moderate means 3-5 points and severe means 5-7 points.

In blood rheology indexes; whole blood high cut viscosity, whole blood low cut viscosity and Polycythemia Vera (PCV) and Erythrocyte Sedimentation Rate (ESR) were measured using LIANG-100 blood viscometer before and after treatment. In serum-related factors; the levels of Prostaglandin E2 (PGE2), 6-Keto-Prostaglandin F1alpha (6-K-PGF1α), Malondialdehyde (MDA), and Superoxide Dismutase (SOD) were determined by enzyme-linked immunosorbent assay in 5 ml of fasting venous blood before and after treatment.

Statistical processing:

Statistical Package for the Social Sciences (SPSS) 23.0 statistical software was used to statistically examine the data's findings. The t-test was used to compare measurement data between groups, and the paired t-test was used to compare measurement data before and after treatment. Measurement data were reported as (s). To compare groups, the Chi-square (χ^2) test was applied to count data, which were reported as (rate). $p<0.05$ was used to indicate that a difference was statistically significant.

RESULTS AND DISCUSSION

When clinical details like age and gender were compared between the two groups, there were no statistically significant differences ($p>0.05$, Table 1). In comparison to the control group, the study group's total treatment effectiveness was higher ($p<0.05$, Table 2). The time to hemostasis, time to blood pressure stabilization and time to relief of abdominal pain were shorter in the research group than in the control group ($p<0.05$, fig. 1).

Prior to treatment, there was no statistically significant difference between the two group's Traditional Chinese Medicine (TCM) syndrome ratings ($p>0.05$); however, both group's scores fell after treatment, with the research group's nine TCM syndrome scores—including one for gastric fullness—being lower than those of the control group ($p<0.05$, fig. 2A-fig. 2I).

Before starting treatment, there were no statistically significant differences between the two groups in terms of whole blood high cut, whole blood low cut, PCV, or ESR ($p>0.05$). Following treatment, the ESR was lower in both groups and was lower in the research group compared to the control group ($p<0.05$, fig. 3A); the whole blood high cut, whole blood low cut, and PCV were also greater in the research group compared to the control group ($p<0.05$, fig 3B and fig. 3C).

Before treatment, there was no statistically significant difference in the levels of PGE2, 6-Keto-PGF1, MDA or SOD between the two groups ($p>0.05$). PGE2, 6-Keto-PGF1 and MDA levels in both groups decreased after treatment, with the research group having lower levels than the control group ($p<0.05$, fig. 4A-fig. 4C), whereas SOD levels in both groups rose, with the research group having higher levels than the control group ($p<0.05$, fig. 4D).

TABLE 1: CLINICAL INFORMATION OF THE TWO GROUPS

Group	n	Gender		Age (years)	Causes of bleeding					Severity		
		Male	Female		Gastric ulcer	Duodenal ulcers	Acute gastric mucosal lesions	Ruptured esophagogastric fundic varices	Gastric polyps	Mild	Moderate	Severe
Research	55	30 (54.55)	25 (45.45)	43.29±3.24	16 (29.09)	14 (25.45)	8 (14.55)	10 (18.18)	7 (12.73)	28 (50.91)	21 (38.18)	6 (10.91)
Control	54	30 (55.56)	24 (44.44)	43.26±3.21	15 (27.78)	14 (25.93)	8 (14.81)	9 (16.67)	7 (12.96)	27 (50.00)	22 (40.74)	6 (11.11)
χ^2 or t	-	0.011		0.049	0.023	0.003	0.002	0.044	0.001	0.009	0.075	0.001
p	-	0.916		0.961	0.879	0.955	0.968	0.835	0.971	0.924	0.785	0.973

TABLE 2: TOTAL EFFECTIVE RATE OF TREATMENT IN BOTH GROUPS [n (%)]

Group	n	Significant	Effective	Ineffective	Total effective
Research	55	28 (50.91)	23 (41.82)	4 (7.27)	51 (92.73)
Control	54	24 (44.44)	18 (33.33)	12 (22.22)	42 (77.78)
χ^2	-	-	-	-	4.862
p	-	-	-	-	0.028

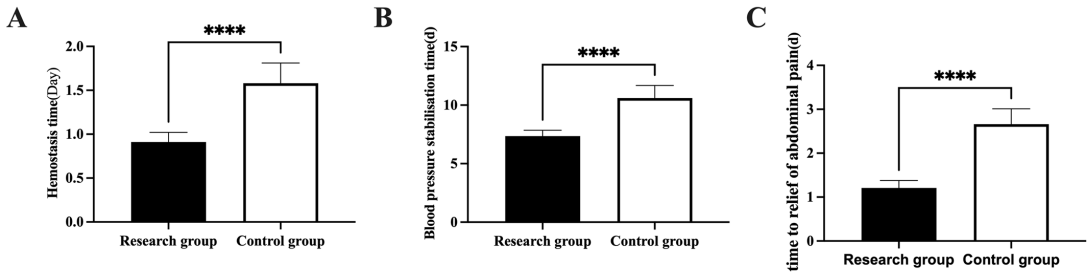

Fig. 1: Comparison of hemostatic effects between the two groups, (A): Comparison of time to hemostasis; (B) Comparison of time to blood pressure stabilization time and (C): Comparison of time to relief of abdominal pain

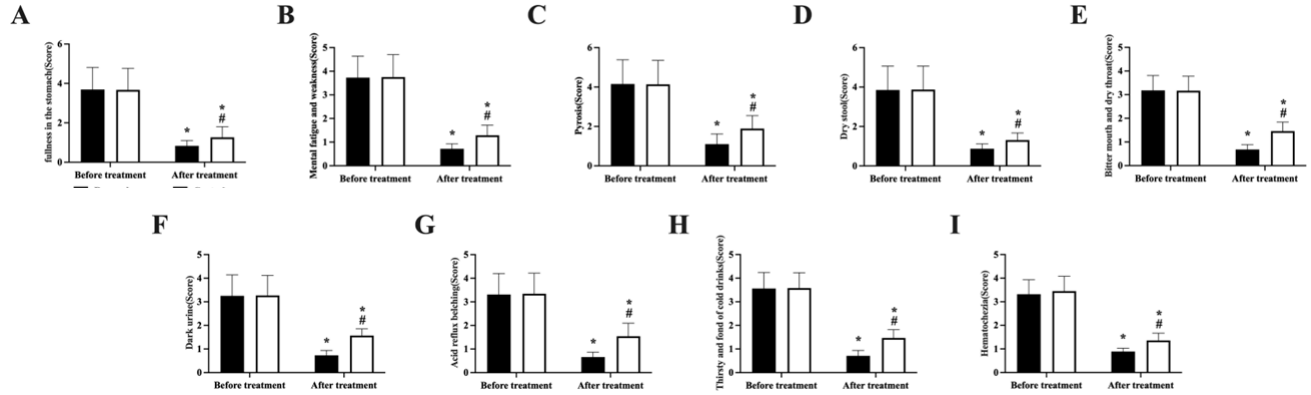

Fig. 2: Comparison of the TCM syndrome scores of the two groups, (A): Comparison of fullness in the stomach; (B): Comparison of mental fatigue and weakness; (C): Comparison of pyrosis; (D): Comparison of dry stools; (E): Comparison of bitter mouth and dry throat; (F): Comparison of dark urine; (G): Comparison of acid reflux belching; (H): Comparison of thirsty and fond of cold drinks and (I): Comparison of hematochezia
Note: (▬): Research group and (▭): Control group

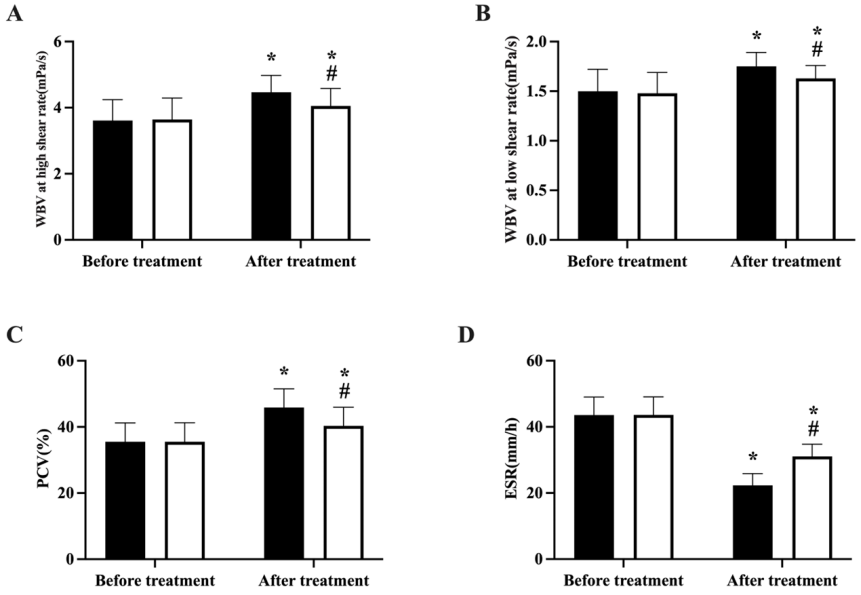

Fig. 3: Comparison of blood rheological parameters between the two groups. (A): Comparison of whole blood high cut viscosity; (B): Comparison of whole blood low cut viscosity; (C): Comparison of PCV and (D): Comparison of ESR
Note: (▬): Research group and (▭): Control group

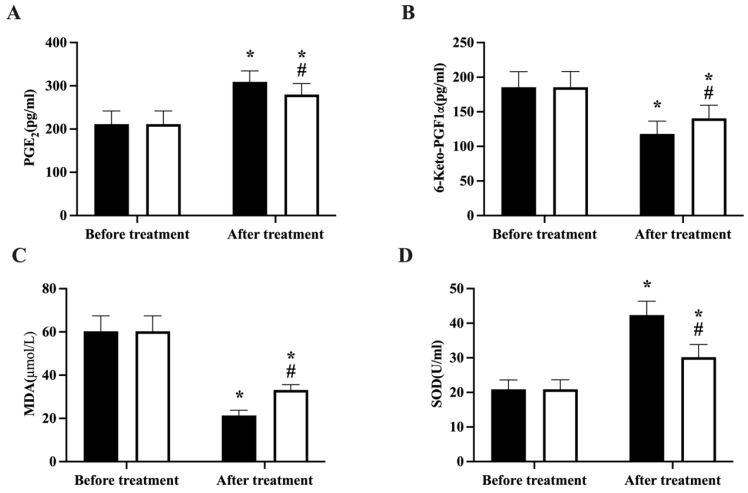

Fig. 4: Comparison of serum-related factors between the two groups. (A): Comparison of PGE2; (B): Comparison of 6-Keto-PGF1α; (C): Comparison of MDA and (D): Comparison of SOD
Note: (▬): Research group and (▭): Control group

The duodenal and stomach's mucosal barriers getting damaged is a contributing factor in the prevalence of upper gastrointestinal hemorrhage and the over-secretion of gastric acid, and upper gastrointestinal hemorrhage is becoming more common both in China and around the world, with a death rate ranging from 8.5 % to 14.5 %. It can be complicated by hemorrhagic shock, which can seriously affect the patient's prognosis[12,13]. The conventional clinical treatment for upper gastrointestinal bleeding is represented by omeprazole, a proton pump inhibitor. Although this drug can be effective, studies have revealed that prolonged use is not recommended for some older or more seriously ill patients because it can increase the risk of gastrointestinal infections[14]. Most studies in China have found that Chinese medicine combined with proton pump inhibitors is more effective and safer in upper gastrointestinal bleeding.

According to TCM, upper gastrointestinal bleeding is mostly caused by internal organ disorders and dysfunction, resulting in Qi and fire rebellion and blood not following the meridians, leading to fire and heat burning, Qi deficiency and blood overflowing outside[15]. According to some researchers, the weakness of the spleen and stomach serves as the disease's root, while phlegm, dampness, and stagnant fire serve as its symptoms. Therefore, the main treatment should be to cool the blood and stop bleeding, dispel blood stasis and disperse nodules[16]. This formula uses large doses of radix et rhizoma Dioscoreae, radix *Aconitum*, radix ginseng, radix Macrocephalae and radix *Achyranthis*, which is a "seven-point tonic for yin", and a "three-point tonic for yang" with radix *cinnamomi*, radix *Glycyrrhiza uralensis*, radix ginger and jujube. On the one hand, Zhigancao decoction is a classic formula for treating "pulse knotting and palpitation", "deficiency labour" and "lung impotence" by Zhang Zhongjing, the sage of medicine. On the other hand, modern research has shown that Zhigancao decoction can both anti-coagulate to prevent thrombotic events and exert a significant hemostatic effect, with a two-way regulatory effect[17]. This shows that Zhigancao decoction is an allopathic medicine for upper gastrointestinal bleeding. Sheng di huang is the dominant herb in Zhigancao decoction and is essential to the formula's effectiveness since it clears heat, cools the blood, nourishes yin, encourages the formation of body fluid, and activates blood stasis[18]. At the same time, roasted licorice can benefit qi and revive the blood vessels; Maitong can moisten the lung and nourish yin, benefit the stomach and produce fluid; dang ginseng can nourish the blood and produce fluid; fire hemp seed can open the lung and invigorate the blood; cinnamon stick can warm the meridians and help yang to transform qi; aconite and jujube can nourish the blood and nourish yin; dried ginger can warm the middle of the body and disperse cold, return yang and open the blood vessels. In the therapy of upper gastrointestinal bleeding, the combination of all the herbs together can benefit qi and warm yang, nourish yin, and stop bleeding, which can stop bleeding, regulate blood pressure, and relieve symptoms with outstanding results. Our study’s findings demonstrated that Zhigancao decoction effectively treats upper gastrointestinal bleeding and has a good synergistic effect with Western medicine. The time to stop bleeding, the

time to stabilize blood pressure, the time to relieve abdominal pain, and the points of various TCM symptoms were all shorter (lower) in the research group after treatment than in the control group.

In our study, we further investigated the mechanism by which Zhigancao decoction as an adjunct to Western medicine in the treatment of upper gastrointestinal bleeding could achieve significant results, both in terms of blood rheology and serum-related factors.

The rheological profile of blood can visually reflect the coagulation function of patients. Patients with upper gastrointestinal bleeding have decreased platelet function, impaired coagulation, decreased blood viscosity, decreased PCV and increased ESR[19]. This study demonstrated that Zhigancao decoction, when combined with Western medicine, can significantly improve blood rheological parameters in patients with upper gastrointestinal bleeding. This is probably because Zhigancao decoction encourages platelet aggregation at the bleeding site. Following therapy, the research group's whole blood high cut, whole blood low cut, and PCV were all greater than those of the control group, while the ESR was also lower.

PCE2 inhibits gastric acid secretion, synthesizes protective substances of gastric mucosa and maintains good blood circulation of gastric mucosa. 6-Keto-PGF1α has the function of inhibiting platelet aggregation and promoting peripheral vasodilation, which are key factors affecting the blood coagulation function of the body and the degree of ulcer bleeding[20]. Both act as synthetic prostaglandins in the gastrointestinal mucosa and are widely present in the gastric and duodenal mucosa, which can effectively reduce the damage to the epithelial cells of the digestive tract and protect the gastric mucosa. At the same time, after the onset of upper gastrointestinal bleeding patients, the tissues and organs are in a state of hypoxia and ischemia, leading to the synthesis of a large number of oxygen free radicals, stimulating lipid peroxidation reactions, and the accumulation of products of oxidative metabolism can produce greater damage to tissues and organs[21]. MDA is an oxidative metabolite with a high synthesis in various hypoxic diseases; SOD is an antioxidant factor, which neutralizes a large number of oxygen free radicals and metabolites after the onset of ischemic-hypoxic injury. According to the study's findings, Zhigancao decoction combined with Western medicine may be able to control PCE2 and 6-Keto-PGF1 in order to lessen epithelial cell damage in the upper gastrointestinal tract and to encourage haemostasis and post-haemostatic healing. After treatment, the research group's levels of PGE2, 6-Keto-PGF1, and MDA were lower than those of the control group, while their levels of SOD were greater; at the same time, it can reduce oxidative stress after the onset of the disease and promote oxidative/antioxidant balance in the body.

The objective conditions revealed that the number of cases included in this study was small, which tended to cause statistical calculation chance. Additionally, the mechanism by which Zhigancao decoction could effectively stop bleeding was not studied in depth. Despite the fact that this study confirmed the significant effect of roasted licorice soup as an adjunct to Western medicine in the treatment of upper gastrointestinal bleeding through several results. In future studies, with a view to offering more practical, educational and guiding opinions for the clinical treatment of upper gastrointestinal bleeding, we will increase the number of cases and conduct a thorough investigation on the mechanism of Zhigancao decoction as a complement to Western medicine in the treatment of upper gastrointestinal bleeding.

Zhigancao decoction can significantly improve the hemodynamic status when used as an adjuvant to conventional medicine in the treatment of upper gastrointestinal bleeding. The body's reduced stress response and the down-regulation of PGE2 and 6-Keto-PGF1 levels may be the mechanism of action.

Conflict of interests:

The authors declared no conflict of interests.

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