

Application of the Method of Promoting Blood Circulation and Removing Blood Stasis in Precancerous Lesions of Gastric Cancer

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Abstract: *Objective* Precancerous lesions are the main risk factors leading to gastric cancer. Therefore, active intervention will help to reduce the incidence rate of gastric cancer. According to the theory of “blood stasis syndrome” in traditional Chinese medicine, the use of the “promoting blood circulation and removing blood stasis” treatment method has achieved good therapeutic effects in the diagnosis and treatment of precancerous lesions of gastric cancer. The method of promoting blood circulation and removing blood stasis includes promoting qi and blood circulation, nourishing yin and blood circulation, detoxifying and activating blood circulation, dispelling dampness and activating blood circulation, etc. Its mechanism of action is to prevent gastric mucosal atrophy, reverse intestinal metaplasia, cut off the process of epithelial neoplasia, inhibit new blood vessel formation, inhibit cancer cell growth, regulate inflammatory factors, delay disease progression, inhibit cell proliferation, and prevent cancer cell growth.

Keywords: Gastric cancer, Gastric precancerous lesions, Promote blood circulation and remove blood stasis, Tumor.

1. Introduction

Gastric cancer is a malignant tumor with high incidence in China and even in the world. Its mortality and incidence rate are very high, second only to lung cancer, and the mortality rate is the second highest. The patients are mainly middle-aged and elderly people. However, in recent years, the trend of gastric cancer is becoming younger and younger [1]. At different stages, there are significant differences in the prognosis of gastric cancer. The five-year survival rate of small and micro gastric cancer is 100%, while the five-year survival rate of early gastric cancer can still be maintained at 90%. However, if it is advanced or late stage, the survival rate will be greatly reduced. Gastric precancerous lesions (GPL) are mainly secondary and accompanied by chronic atrophic gastritis. Gastric mucosal atrophy and intestinal metaplasia belong to the precancerous state (CAG), while gastric intraepithelial neoplasia (GIN) belongs to precancerous lesions. At present, Western medicine treatment for primary gastric cancer has problems such as high toxicity and side effects, high recurrence rate, and poor quality of life. For patients diagnosed with mucosal tumors or abnormal gastric epithelial hyperplasia, endoscopic mucosal resection surgery is indicated and not suitable for most patients. Previous studies have shown that traditional Chinese medicine can significantly improve PLGC and reduce the incidence rate of gastric cancer by intervening or reversing its canceration process [4] [5] [6]. Regarding the clinical treatment of PLGC with the method of promoting blood circulation and removing blood stasis, the therapeutic effect has been quite good. Therefore, drawing on the research results of various experts, this article summarizes the treatment methods of PLGC, providing clinical reference for the treatment of PLGC with the method of promoting blood circulation and removing blood stasis.

2. Origin of Traditional Chinese Medicine Theory of PLGC

Chinese medical practitioners throughout history have not given a specific name to gastric cancer, which is mostly classified as “epigastric pain”, “nausea”, “accumulation” and other categories. In traditional Chinese medicine, gastric cancer is a systemic disease related to the whole body, often caused by improper diet, emotional disorders, fatigue, internal injuries, or external pathogens, resulting in an imbalance of yin and yang in the body, dysfunction of organs and meridians, and a series of pathological changes such as food stagnation, qi stagnation, blood stasis, phlegm accumulation, and the accumulation of pathogenic toxins, which ultimately lead to cancer. The book “Synopsis of the Golden Chamber” first mentions blood stasis, and its “Diagnosis and Treatment of Blood Stasis in the Chest due to Trembling, Vomiting, and Bleeding” chapter 16 states that “the patient has a full chest, withered lips, green tongue, and dry mouth, but wants to rinse water but does not want to swallow, no cold or heat, slightly large and delayed pulse, and a dissatisfied abdomen. They say they are full, indicating the presence of blood stasis”, which is a symptom; The patient is in a hot state, full of annoyance, with a dry and thirsty mouth, and no heat in their pulse. This is Yin Fu, blood stasis, and should be treated immediately; The eleventh chapter of the “Five Organs Wind Cold Accumulation Disease Pulse Syndrome and Treatment” states that “if the accumulation occurs, the organs will not move; if the accumulation occurs, the organs will also be affected”, which is a disease. Modern research has shown that the proliferation of endothelial cells in the gastric mucosal layer and submucosal layer leads to narrowing of the vascular lumen, resulting in reduced blood supply to local tissues and prolonged hypoxia of cells, which can easily cause the occurrence and development of tumors, consistent with the

traditional Chinese medicine concept of “blood stasis” [8]. The above research suggests that blood stasis is an important pathogenesis of primary gastric cancer. Modern studies on syndrome differentiation have also shown that blood stasis is an important syndrome differentiation factor in PLGC, especially in CAG, and the method of promoting blood circulation and removing blood stasis is a commonly used treatment for PLGC [9] [10].

3. The Specific Application of the Method of Promoting Blood Circulation and Removing Blood Stasis

Traditional Chinese Medicine believes that the occurrence of PLGC is related to dietary fatigue, emotional disorders, liver depression and qi stagnation, poor rise and fall of the spleen and stomach, loss of clear and rising spleen, loss of gastric drainage, and long-term damage to the spleen and stomach. Or congenital deficiency, spleen and stomach deficiency, and inability to transport and transform [11]. The disease is caused by qi stagnation, toxin heat accumulation, yin deficiency and blood stasis, and damp heat accumulation. Therefore, the treatment methods for the above disease mechanisms are as follows:

3.1 Qi and Blood Circulation Method

The first chapter of the Yellow Emperor's Inner Canon elaborates on the important significance of “qi” and “qi” and “communication”, just as the “Su Wen · Liu Wei Zhi Da Lun” says: “Without going in and out, there can be no growth, strengthening, or aging; without ascending and descending, there can be no growth, transformation, or collection. The spleen and stomach are the central organs for the rise and fall of qi. The spleen is responsible for regulating and releasing qi, while the stomach reduces turbidity. Generally speaking, if the gastric motility is normal, it can push the initially digested chyme towards the small intestine, guide the waste downwards, and maintain normal digestion and absorption functions. If the stomach qi cannot be lowered, symptoms such as abdominal distension and pain, hiccups and vomiting, loss of appetite, constipation, etc. may occur. As stated in the “Great Confusion Theory” of the “Ling Shu”: “When the stomach qi is reversed, the stomach is cold, so there is no appetite.” Stomach coldness, loss of appetite, poor diet, and insufficient nutrition can affect various functions of the body. The book “Su Wen: On the Theory of Reverse Regulation” states: “Yangming is the pulse of the stomach, and the stomach is the sea of the six organs. Its qi also descends, and the yang is clear and reversed. It cannot follow its path, so it cannot lie down.” It is believed that the stomach's qi pulse cannot rise normally, resulting in restless sleep. The book “Su Wen · Xuan Ming Wu Qi Pian” states: “When the stomach is in a state of qi reversal, it becomes fear.” It can be seen that when the stomach qi is in a state of upward reversal, it not only causes hiccups, but also affects people's emotions and creates a feeling of panic. Qi stagnation is a prerequisite for the onset of PLGC. Qi is the leader of blood, and blood is the mother of qi. Qi stagnation causes blood to stagnate in the pulse, further leading to stagnation of qi and blood, which in turn affects the onset of PLGC. Therefore, the method of promoting qi circulation and blood circulation should be used to promote blood circulation throughout the body, thereby

preventing the progression of PLGC. In clinical practice, the method of promoting qi circulation, clearing heat, and activating blood circulation is adopted, with Huangqi, Codonopsis pilosula, Danshen, Curcuma zedoaria, Scutellaria baicalensis, Rehmannia glutinosa, Coix seed, Hedyotis diffusa, Xianhe grass, and roasted licorice as the main formulas. Dandelion and Huanglian are added to clear heat; The combination of promoting blood circulation and unblocking meridians with red peony and Chuanxiong has a significant therapeutic effect [14].

3.2 Methods of Promoting Blood Circulation and Detoxification

As stated in the book “Ling Shu: The Beginning of All Diseases”, “Even in the midst of deficiency and evil, if a person stays and does not leave, they will be passed down to the meridians... if they stay in the meridians, they will be missed and not leave, and they will accumulate after resting.” The research team found in the early stage that turbidity, toxicity, and stasis are key links in the occurrence, development, and persistence of CAG. He also proposed the hypothesis of the pathogenesis of “toxic damage to the stomach meridian”, that is, “the accumulation of toxic pathogens in the stomach meridian” is an important cause of chronic gastritis [16]. In clinical practice, common symptoms include epigastric pain, inability to press, and even more severe pain at night. There are also petechiae or ecchymoses under the tongue, and the sublingual veins are blue and purple, with smooth and stringy veins. In terms of treatment, the main focus is on promoting blood circulation, removing blood stasis, unblocking meridians, and detoxifying. Treatment includes the use of Xiaoxiao San and Danshen Yin. Medications that can be taken under the guidance of a doctor include Danshen, Sharen, Puhuang, Curcuma, and Curcuma. In addition, medications such as Solanum nigrum and Corydalis yanhusuo can also be taken under the guidance of a doctor. Commonly used blood activating, blood stasis removing, and pain relieving drugs in clinical practice include Danshen, Curcuma, Curcuma, Angelica sinensis, and Longkui and snake berry promote blood circulation and remove blood stasis, detoxify and fight cancer. Modern research shows that turmeric has anti-tumor, antiplatelet aggregation, antibacterial, anti-inflammatory and other effects, especially with special inhibitory effects on tumors [18]. Our previous research found that the extract of traditional Chinese medicine Danshen has significant anti-cancer activity, while Chuanxiong has the effects of improving microcirculation, inhibiting platelet aggregation, enhancing hemodynamics, inhibiting thrombosis, activating fibers, and promoting gastrointestinal circulation [19].

3.3 Yin Nourishing and Blood Activating Methods

Therefore, the five senses cannot be damaged. If they are damaged, they will lose their vital energy, and if they lose their vital energy, they will die. The “Treatise on the Origins of Various Diseases” states: “If the camp is not smooth, there is no distinction between yin and yang, and qi and blood are not smooth.” The “Synopsis of the Golden Chamber” also states: “Those who are dissatisfied are blood stasis.” The ancients said: “If the yin and yang meridians are balanced, the essence will be calm.” “Harmony of qi and blood prevents the

birth of all diseases.” It highlights the most fundamental relationship within the human body, which is the overall balance and coordination of the body. A formula for nourishing yin and promoting blood circulation is composed of eight traditional Chinese medicines, including sand ginseng, *Ophiopogon japonicus*, Shengdi, Goji berry, *Angelica sinensis*, *Melia sinensis*, Wulingzhi, and Puhuang. In the formula, sand ginseng nourishes yin and blood, replenishes deficiency and damages yin, and has significant therapeutic effects; *Ophiopogon japonicus*, *Radix Rehmanniae*, and Goji berries each have the effects of nourishing yin and kidney, nourishing yin and benefiting the stomach. *Angelica sinensis* is a product that nourishes blood and promotes blood circulation, while Wulingzhi and Puhuang can promote blood circulation and remove blood stasis. The eight herbs complement each other, jointly promoting the effects of nourishing yin and activating blood circulation.

3.4 Dampness Dispelling and Blood Activating Methods

The pathological basis of PLGC is spleen and stomach deficiency, and dampness, turbidity, and blood stasis run through the entire process of the disease, which is an important link in the development and progression of the disease. It is the result of the long-term existence of spleen disease, which has gone through multiple stages. As early as in the “Treatise on Cold Damage: Pulse Differentiation Method”, it was mentioned that “if the middle burner is not treated, the stomach qi will rush upwards, the temperament will not change, the stomach will be turbid, the Rongwei system will be blocked, and blood coagulation will not flow.” This is a description of the characteristics of spleen and stomach diseases that are prone to cause blood stasis. The Compendium of Materia Medica “records:” Danshen, with the same functions as the four substances, can dispel blood stasis to generate new energy, is good at treating wind and dispersing knots, and has a calm nature to promote blood circulation; Shi Jian is known for its ability to penetrate bitter and pungent waters, enter the liver and spleen meridians, promote blood circulation and remove blood stasis, clear heat and detoxify, reduce swelling and phlegm, disperse nodules and relieve pain, and achieve the functions of promoting blood circulation and removing blood stasis, unblocking collaterals and dispersing nodules. According to the “Essentials of Materia Medica Preparation”, “its nature is good at walking, it can clear the five viscera, and pass through the twelve meridians”; Sheng Yi Ren has a sweet taste. According to the “Compendium of Materia Medica”, “Yi Yi Ren has a dry nature that can remove dampness, a sweet taste that can enter the spleen and supplement the spleen, and a light taste that can penetrate dampness”. Modern pharmacological research has shown that Yi Yi Ren has the effect of inhibiting tumor cell proliferation and inducing tumor cell apoptosis [24].

4. Research on the Main Ways of Treating PLGC with the Method of Promoting Blood Circulation and Removing Blood Stasis in Modern Medicine

In recent years, the therapy of promoting blood circulation and removing blood stasis has been widely used in clinical

practice and has achieved good results. The research results are summarized as follows:

4.1 Preventing Gastric Mucosal Atrophy, Reversing Intestinal Metaplasia, and Cutting Off the Process of Intraepithelial Neoplasia

From gastritis to gastric cancer, it goes through four stages: superficial gastritis/non atrophic gastritis chronic atrophic gastritis intestinal metaplasia epithelial neoplasia gastric cancer. Blocking any of these steps can effectively prevent and treat gastric cancer. There is literature indicating that blood activating and stasis removing drugs such as Chuanxiong, Curcuma, and Danshen can increase DNA synthesis in gastric cancer cells, promote cell proliferation, and inhibit or reverse the occurrence of gastric cancer [25]. The role of blood activating and stasis removing drugs such as *Paeonia lactiflora* and *Panax notoginseng* in the treatment of chronic gastritis is very obvious, which has the effects of promoting blood circulation, improving local ischemia, hypoxia and mucosal microcirculation, promoting the regeneration of atrophic glands, and promoting the absorption of inflammation [26]. A study has treated 25 patients with CAG of Qi deficiency and blood stasis type with modified Yiqi Huoxue Tongluo formula, and found that the addition of a large dose of Huangqi in the formula enhances the effect of tonifying the body [27]. Research has found that the effective component of *Astragalus membranaceus*, Astragalosides, can regulate programmed cell death of gastric epithelial cells through the Kras/p53 signaling pathway, thereby delaying the development of precancerous lesions in gastric cancer [28]. Professor Cha [29] randomly divided 60 patients with CAG precancerous lesions into a treatment group of 30 cases (oral administration of Yiqi Huayu Jiedu Granules) and a control group of 30 cases. The treatment lasted for 12 weeks, and the patients were followed up for 12 weeks. Gastroscopy, pathology Hp infection and EGF changes. The research results showed that the treatment group had a significant therapeutic effect, with better gastroscopy, pathology, Hp infection, and EGF changes than the control group. It inhibited gastric mucosal atrophy and greatly improved the pathological changes of intestinal metaplasia and dysplasia.

4.2 Inhibit the Formation of New Blood Vessels and Suppress the Growth of Cancer Cells

Our previous research has shown that the pathogenesis of blood stasis syndrome is essentially due to insufficient oxygen supply. Under local hypoxic conditions, blood cell stress increases, endothelial cell proliferation occurs, and tumor neovascularization is induced. Blood activating and stasis removing drugs can improve tissue ischemia and hypoxia by promoting gastric mucosal microcirculation, inhibiting endothelial cell proliferation, reducing tumor angiogenesis, and lowering the possibility of cancer [30]. The occurrence, development, and metastasis of tumors cannot be separated from cell proliferation, and abnormal proliferation of blood vessels is closely related to the occurrence and development of tumors [31]. Research has found that the pathogenesis of “blood stasis” is essentially hypoxia. The occurrence of blood stasis is closely related to blood circulation (especially microcirculation) and lymphatic circulation. The main function of blood circulation is to exchange substances with

blood supply cells, including both oxygen supply and metabolic elimination. Hypoxia is caused by various pathological reasons leading to blood circulation disorders. However, studies have shown that the hypoxia supply in tumor tissue is closely related to the formation of tumor blood vessels [32]. Previous studies by Huang Yilun et al. [33] have shown that Turopatide and Triptolide (also known as Turopatide) can significantly inhibit the proliferation, migration, and lumen formation of vascular endothelial cells, and have good anti endothelial function. Further research has found that resveratrol from *Tripterygium wilfordii* can induce ECV304 to remain in the S phase and inhibit its proliferation; Meanwhile, resveratrol from *Tripterygium wilfordii* can induce apoptosis in ECV304, thereby affecting the normal function of blood vessels [34].

4.3 Regulating Inflammatory Factors and Delaying Disease Progression

Inflammatory factors play an important role in the occurrence and development of precancerous lesions in gastric cancer. IL-1 β is a cytokine with pro-inflammatory effects that can effectively inhibit the secretion of gastric acid, leading to atrophy of the gastric mucosa. In the gastric mucosal inflammatory response caused by Hp infection, the relationship between the two is enhanced, while also reducing the clearance rate of inflammatory substances, resulting in cell apoptosis [35]. Interleukin-8 (IL-8) is a cytokine that can attract neutrophils and is an important factor in the occurrence and development of gastric cancer, which has been confirmed by research [36]. NF - α not only promotes apoptosis of gastric cancer cells, but also effectively inhibits gastric acid secretion, exacerbates Hp infection, and accelerates gastric mucosal atrophy [37]. Our research group found that after 12 weeks of intervention with the Huoxue Huayu Jiedu Formula, the serum levels of IL-1 β , IL-8, and TNF- α in rats significantly decreased, suggesting that this formula may exert anti-inflammatory effects by downregulating signaling pathways such as IL-1 β , IL-8, and TNF - α [38].

4.4 Inhibit Cell Proliferation and Anti-cancer Cell Growth

Over the years, clinical studies have found that blood activating and stasis removing drugs represented by turmeric can significantly inhibit the expression of oncogenes and suppress the growth of tumor cells, thereby reducing tumor invasion and metastasis. Scorpion extract has a significant inhibitory effect on tumor cell proliferation, and its effect on tumor cells is mainly achieved by inhibiting the respiration of cancer cells [39]. Previous studies have found that curcumin can significantly inhibit the growth of MKN45 cells, reduce their migration and invasion abilities, and promote apoptosis. This effect may be achieved by downregulating the Wnt3a/ β -catenin/EMT signaling pathway, Bcl-2 family, and caspase pathway [40]. Further research has found that high expression of circ_0056618 can significantly enhance the proliferation, migration, and invasion ability of gastric cancer cells, and can inhibit cell cycle arrest and apoptosis; Curcumin reverses the promotion of gastric cancer growth by upregulating miR-194-5p and circ_0056618 [41]. The unique properties of Ranunculaceae plants include clearing heat, detoxifying, eliminating phlegm, and dispersing nodules. Their active

ingredients can directly kill cancer cells and inhibit their infiltration and metastasis [42]. Half branch lotus has the functions of clearing heat and detoxifying, dispersing blood stasis and fighting cancer. It contains various anti-tumor components, and its mechanism of action includes inhibiting metastasis and differentiation, inducing autophagy of cancer cells, etc. [43].

5. Summary

Ye Tianshi proposed that 'prolonged illness inevitably leads to blood stasis', The prolonged and recurrent course of PLGC is the material basis for the occurrence and development of blood stasis. At the same time, due to insufficient positive energy, it is unable to provide power for the blood, and it may also be caused by qi stagnation, phlegm dampness, and heat toxin stagnation, resulting in poor qi and blood circulation, leading to gastric congestion. Clinically, epigastric pain is also the main manifestation, with pain in a fixed location or worsening at night, dull tongue texture, bruising and spots, astringent pulse, and floating pulse. Therefore, in the treatment of this disease, the first step should be to use the method of promoting blood circulation and removing blood stasis, and then choose corresponding treatment methods for different causes.

6. Expectation

The method of promoting blood circulation and removing blood stasis has sufficient theoretical support in the treatment of PLGC and has achieved significant results in clinical practice. However, there are still many problems, such as large differences in the compatibility of blood circulation and removing blood stasis formulas, insufficient research on the mechanism of action of blood circulation and removing blood stasis on PLGC, lack of large sample RCT data support, small sample size, and the need for further large-scale, high-quality, multi center clinical research, combined with animal models for verification, in order to lay the foundation for the clinical application of blood circulation and removing blood stasis method.

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