Review Article

Research progress of traditional Chinese medicine in the treatment of gastric mucosa injury caused by long-term use of low dose aspirin in patients with coronary heart disease

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Abstract: Aspirin is widely used in the treatment and prevention of coronary heart disease (CHD). It plays an important role in anti-platelet aggregation by inhibiting the activity of cyclooxygenase-1 (COX-1). On the other hand, the decrease of COX-1 activity inhibits the production of prostaglandin (PG) in gastric mucosa, which leads to the decrease of gastric mucosal blood flow and the weakening of mucous barrier. That makes the gastric mucosa more vulnerable to injury. We usually treat gastric mucous injury caused by long-term use of low-dose-aspirin (LDA) with drugs that inhibit gastric acid secretion. However, these drugs cannot improve gastric mucosal blood flow and the effect of gastric mucous barrier. And the long-term use of these drugs can lead to a variety of adverse reactions, such as dyspepsia, osteoporosis, nutritional deficiency and so on. This paper reviews the research progress of traditional Chinese medicine (TCM) in the treatment of gastric mucosa injury caused by LDA. It was found that *Panax quinquefolius* (*Xiyangshen*) saponins, Astragaloside A, *Dendrobium officinale* (*Tiepishihu*) polysaccharide, *Bletilla Striata* (*Baiji*), Jinghua Weikang capsule, Danhong injection and other TCM components or preparations can increase the level of PG in gastric mucosa and increase the blood flow of gastric mucosa, so as to improve the effect of gastric mucous barrier. This provides a certain idea for the prevention and treatment of gastric mucosa injury caused by long-term application of LDA in patients with CHD.

Keywords: coronary disease; aspirin; stomach; traditional Chinese medicine (TCM)

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Introduction

Although the treatment of atherosclerotic cardiovascular disease (ASCVD) has improved greatly in recent decades, it is still the main cause of morbidity and mortality globally (1). Coronary heart disease (CHD) is the most common cause of death in all patients with ASCVD (2). It's reported that the number of patients with CHD in China has reached 11 million, and will continue to grow in the next 10 years (3). At present, low-dose-aspirin (LDA, 75~150 mg/d) is widely used in the treatment and prevention of cardiovascular diseases (4). For example, the American Heart Association (AHA) recently recommended that all adults aged 40 to 70 with a high risk of ASCVD and no significant risk of bleeding should take aspirin (75–100 mg/d) for primary prevention of cardiovascular diseases (1). The European College of Cardiology (ESC) recommends that the patients with stable angina pectoris should take aspirin for 75–150 mg/d (5), the patients with acute coronary syndrome presenting or not ST-segment elevation should take aspirin for 75–100 mg/d unless contraindication (2,6).

Although LDA can reduce the incidence of acute cardiovascular events in patients with CHD (7), its long-term use can lead to many side effects (8). Studies have shown that aspirin increased the risk of gastroduodenal ulcer by 2 to 4 times (9,10) and the relative risk of upper gastrointestinal bleeding by 1.7 times (11). We usually treat gastric mucous injury caused by LDA with drugs that inhibit gastric acid secretion (12). However, these drugs cannot improve gastric mucosal blood flow and the effect of gastric mucous barrier. Moreover, the long-term use of these drugs can lead to a variety of adverse reactions, such as dyspepsia, osteoporosis, nutritional deficiency and so on (13). In this paper, the research progress of traditional Chinese medicine (TCM) in the treatment of gastric mucosal injury induced by LDA is reviewed, which provides some ideas for the prevention and treatment of gastric mucosal injury caused by long-term application of LDA in patients with CHD.

Epidemiology of gastric mucosal injury caused by aspirin

Long-term use of aspirin can lead to gastrointestinal mucosal injury, bleeding, kidney injury, asthma, allergy and other adverse reactions, among which gastric mucosal injury and bleeding are the most common (8). Studies have shown that aspirin increased the risk of gastroduodenal ulcer by 2 to 4 times (9,10). A study combined with data from 14 randomized controlled trials showed that patients who took LDA had a risk of massive gastrointestinal bleeding 1.61 to 2.66 times higher than those in the placebo group (14). In an observation of the risk of upper gastrointestinal bleeding, a cohort study in Denmark showed that the relative risk of upper gastrointestinal bleeding caused by LDA was 2.2 to 2.9 times higher than that of the blank control group (15). A Japanese study found that patients over the age of 70 who took aspirin had a 1.32 to 2.66 times higher risk of upper gastrointestinal bleeding than those in the placebo group (16).

Fifteen percent of all patients who took LDA developed upper gastrointestinal symptoms such as acid regurgitation, heartburn, stomach distension, hiccups, nausea, etc. (17). However, this was not significantly associated with upper gastrointestinal ulcers or bleeding (18). Previous studies have shown that 11% of patients who took LDA for a long time were observed gastrointestinal ulcers under endoscopy, but 80% of them did not show obvious gastrointestinal discomfort (10). Another study found that 47.8% of patients with no upper gastrointestinal symptoms after 3 months of LDA treatment developed gastroduodenal ulcers or erosion, of which gastroduodenal erosion accounted for about 2 to 5 (19). For patients with gastric erosion, the continued use of aspirin may further lead to gastric ulcer and even gastric bleeding (20). Therefore, for asymptomatic patients who take LDA for a long time, we also need to be vigilant in preventing gastrointestinal ulcers and bleeding.

Mechanism of antiplatelet aggregation effect and gastrointestinal injury of aspirin

In 1971, John Vane first discovered the inhibitory effect of aspirin on prostaglandin (PG) synthesis (21), which ushered in a new era for aspirin in the prevention and treatment of cardiovascular and cerebrovascular diseases. However, it was found that the inhibitory effect of aspirin on PG synthesis was closely related to the inhibition of cyclooxygenase (COX) activity (22). COX can be divided into two subtypes: COX-1 and COX-2, and these two subtypes are expressed differently in different cells. Among them, COX-1 was mainly expressed in platelets and gastric mucous membrane cells, and COX-2 was mainly expressed in renal cells, vascular endothelial cells and neutrophils (8). Aspirin can acetylate serine residues in the active center of platelet COX, inhibit arachidonic acid metabolism to produce prostaglandin I2 (PGI2) and thromboxane A2 (TXA2), and finally plays an anti-platelet aggregation effect (4,23).

The injury of upper gastrointestinal mucosa induced by aspirin is mainly related to both local effect and systemic effect (18). Local effect means that aspirin, as a weak acid, can directly act on the phospholipid layer of gastric mucosa, which maintains non-ionizing and lipophilic activity in the strongly acidic gastric cavity, and then damages the gastric mucosa (19). The systemic effect means that aspirin can decrease the production of PG, mucous blood flow and epithelial mucus secretion, which makes the gastric mucosa more vulnerable to exogenous and endogenous substances, such as gastric acid and pepsin, by inhibiting the activities of COX-1 and COX-2 in gastric mucosa through acetylating the serine of the active center of COX (24-26). In addition, the injury of gastric mucosa induced by aspirin is closely related to inflammatory reaction and oxidative stress. The research showed that the level of tumor necrosis factor-α (TNF-α) in plasma was significantly increased in rats with gastric mucosal injury induced by aspirin (27). TNF-α can trigger the release of other inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1β (IL-1β), increase the aggregation of neutrophils, and then cause gastric mucosal

damage (28). At the same time, it can promote the apoptosis of gastric mucosal cells by increasing the expression of caspase-3 (29). Inflammatory factors can mediate the expression of inducible nitric oxide synthase (iNOS), which increases the production of reactive oxygen species (ROS) *in vivo* (30). ROS can make lipid peroxide and decrease the integrity of cell membrane, which leads to gastric mucosal injury for its high chemical reaction (31). Mahmoud found that aspirin can increase the content of malondialdehyde (MDA), a marker of lipid peroxide in gastric mucosal cells, suggesting that aspirin can promote the injury of gastric mucosa by inducing oxidative stress (12).

Clinical study on gastric mucosal injury induced by aspirin with TCM

According to the clinical manifestations of gastric mucosal injury, it can be classified into the categories of "Stomachache", "Noise" and "Acid swallowing" in TCM. According to the characteristics of symptoms, it can be divided into Ganweibuhe, Piweixuhan, Piweishire, Weiyinbuzu, Weiluoyuzu and other syndrome types (32). A study on syndrome differentiation of TCM was carried out in patients who took LDA for a long time and developed symptoms of upper gastrointestinal (32). This study showed the distribution characteristics of TCM syndromes in patients with gastrointestinal bleeding as follows: Piweishire (37.7%) > Weiyinbuzu (17.9%) > Ganweibuhe (17.0%) > Weiluoyuzu (15.1%) > Piweixuhan (12.3%). Moreover, the degree of gastrointestinal injury in patients with Piweishire syndrome was more serious than that in other syndromes, which suggested that patients with Piweishire syndrome were more likely to suffer from upper gastrointestinal injury and bleeding during aspirin use.

In clinical research, Zhong (33) found that the combination of TCM dialectical treatment and western medicine treatment could promote mucous membrane healing, improve the cure rate of gastric ulcer, reduce the adverse reactions during treatment and decrease the recurrence rate of gastric ulcer after 1-year follow-up. Moreover, it can reduce the level of TNF-α, IL-6 and other inflammatory factors in serum (33). Wang (34) found that the combination of Danhong injection could not only increase the antiplatelet aggregation effect of aspirin, but also decrease the activity of pepsin, and promote the secretion of gastric mucus. It could also increase the contents of plasma Catalase (CAT), Glutathione peroxidase (GSH-Px) and Superoxide Dismutase (SOD), which could protect the gastric mucosa by enhancing the antioxidant capacity, and reducing the content of ROS in the body.

Basic study on gastric mucosal injury induced by aspirin with TCM

In the study of TCM compound, Dong (35) found that Jinghua Weikang capsule, which composed *ysphania ambrosioides (Tujingjie)* and *Adina pilulifera (shuituanhua)* extract, could significantly reduce the area of gastric ulcer induced by aspirin in mice. This effect was related to the inhibitory effect of the drug on the secretion of thromboxane B2 (TXB2) and the increase of the level of 6-keto-prostaglandin F1α (6-keto-PGF1α) in gastric mucosa. TXA2 can be rapidly hydrolyzed into stable TXB2, and PGI2 can be decomposed into 6-keto-PGF1α *in vivo* (36). Therefore, the detection of TXB2 and 6-keto-PGF1αlevels can evaluate the levels of TXA2 and PGI2 in the body. Chen (37) found that Jianwei mixture, which composed of *Astragalus propinquus* (Huanqi), *Atractylodes macrocephala* (Baizhu), *Cynanchum otophyllum* (Baishao), *Polygonatum sibiricum* (Huangjing), *Salvia miltiorrhiza Bge* (Danshen), *Pinellia ternata* (Banxia), *Panax notoginseng* (Sanqi), *Scutellaria baicalensis Georgi* (Huangqin), *Glycyrrhiza uralensis Fisch* (Gancao) and so on, could also reduce the secretion of TXB2 in gastric mucosa, increase the content of 6-keto-PGF1α and the regional blood flow of gastric mucosa. Luo (38) found that the levels of IL-1β and TNF-α in serum and the level of NOS in gastric mucus were increased in the rat model of gastric mucosal injury caused by aspirin. But the application of Jiawei Sijunzi decoction could reduce the level of these inflammatory factors, and promote the repair of gastric mucosal injury caused by aspirin. According to the basic study (39), it was found that Danhong injection could increase the activities of CAT, GSH-Px and SOD in gastric mucosa, improve the secretion of gastric mucus, decrease the level of MDA and the activity of pepsin, so as to maintain the integrity of gastric mucous barrier. Meanwhile it could also improve the inhibition rate of aspirin on COX-1 (39).

In the study of TCM monomer, Gao (40) found that *Bletilla Striata* (Baiji) could effectively reduce the injury of gastric mucosa induced by aspirin in rats, which was related to the decrease of serum TNF-α, IL-6 and endothelin (ET) levels, and the increase of prostaglandin E2 (PGE2) level in gastric mucosa. Ding (41) found that *Zingiber officinale Roscoe* (Shengjiang) could also play a protective role in gastric mucosa by decreasing the levels of plasma inflammatory

cytokines TNF-α and IL-1β in rats, and this effect has nothing to do with the inhibition of gastric acid secretion. Kou (42) found that *Panax quinquefolius* (Xiyangshen) saponins could alleviate the injury of gastric mucosa induced by double antiplatelet therapy. He suggested that its mechanism might be related to the inhibition of TXB2 activity and the increase of 6-keto-PGF1α in plasma and COX-2, PGE2 in gastric mucosa. Yang (43) and Fan (31) found that *Dendrobium officinale* (Tiepishihu) polysaccharide and astragaloside A could increase the level of PGE2 in gastric mucosa. At the same time, it could reduce the damage of human gastric epithelial cells (GES-1) induced by aspirin, so as to give full play to the protective effect of gastric mucosa. Li YW (44) found that total flavonoids of *Glycyrrhiza uralensis Fisch* (Gancao) could also inhibit GES-1 apoptosis induced by aspirin, and suggested that this effect was related to the inhibition of ERK1/2 signaling pathway.

Discussion

By summing up the above studies, we can find that TCM can effectively prevent and treat gastric mucosal injury induced by aspirin, and its mechanism is mainly related to increasing the secretion of PG in gastric mucosa and inhibiting the apoptosis of GES-1. At the same time, it is related to the reduction of oxidative stress and the level of inflammation.

GES-1 and gastric mucus secreted by the upper layer of the gastric mucosa form a gastric mucous barrier to protect the submucous cells from the erosion of gastric acid and pepsin, and to resist the invasion of bacteria and microorganisms, which plays an important role in maintaining the normal physiological function of the stomach (45). PG can increase gastric mucous blood flow and promote the secretion of gastric mucus and HCO^-_3, thus improving the effect of gastric mucous barrier (46). However, aspirin can inhibit the secretion of PG in gastric mucosa, thus weakening the barrier of gastric mucosa and making it more vulnerable to exogenous and endogenous substances (24-26). It was found that Jinghua Weikang capsule, Jianwei mixture, Danhong injection and other TCM preparations, as well as Panax quinquefolium, Baihe, Dendrobium candidum and other ingredients of TCM, could increase the synthesis of PG in gastric mucosa, increase the blood flow of gastric mucosa, improve the effect of gastric mucous barrier, so as to reduce the gastric mucous injury caused by aspirin.

Moreover, oxidative stress is an important factor in gastric mucosal injury (47). ROS can cause lipid peroxide and decrease the integrity of cell membrane, which leads to gastric mucosal injury (31). MDA is the end product of unsaturated fatty acid oxidation, and its content can reflect the degree of oxidative stress *in vivo* (48). TNF-α and IL-6, as important inflammatory cytokines, are also involved in the injury process of gastric mucosa (49). According to the above results, it can be found that TCM can increase the content of antioxidant enzymes such as SOD, CAT and GSH-Px, decrease the level of TNF-α, IL-6, IL-1βand other inflammatory factors. That means it can protect gastric mucosa by reducing the level of oxidative stress and inflammatory reaction.

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