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Advances in the Treatment of Post-cholecystectomy Diarrhoea based on Changes in Intestinal Flora

Chengyan Ma[1], Yizhuo Gao[1], Lingyan Chen[1], Tao Yu[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 710003, Shaanxi, China
[2]Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Post cholecystectomy diarrhoea (PCD) is one of the common complications after cholecystectomy, which is characterised by urgency of defecation, increased frequency of defecation, and often during the day. Although its pathogenesis is complex, after cholecystectomy, the diversity and abundance of bacterial flora are significantly altered, and intestinal microecological imbalance plays a major role in the pathogenesis of PCD, and the regulation of intestinal flora is an important means of treatment in the treatment of PCD. In this paper, we review the research progress of PCD treatment based on the alteration of intestinal flora.***

Keywords: Cholecystectomy, Intestinal flora, Post-cholecystectomy diarrhoea, Probiotics, Faecal transplants, Chinese medicine treatment**.**

1. Introduction

Gallstone disease is one of the most common digestive disorders, with a prevalence of about 5% to 22% [1], The treatment of choice for patients with symptomatic gallbladder stones is cholecystectomy (PC). However, in clinical observation, about 5% to 40% of the postoperative population will develop post cholecystectomy syndrome [2], in which diarrhoea is an important form of manifestation, clinically manifested as urgency to defecate and increase in the frequency of defecation. Ribas Blasco et al. [3], found that ≥50% of patients with cholecystectomy developed abnormal defecation habits, and the symptoms of 23% of them remained unrelieved after six months, and there is a trend of high prevalence and chronicity of PCD. The pathogenesis of PCD is complex, YoonWJ and other scholars [4] believe that, cholecystectomy changes the flow of bile into the intestinal tract, the enterohepatic circulation of bile acids, which in turn induces PCD. However, among the many pathogenic mechanisms, the alteration of the intestinal flora occupies a significant position. Currently, more and more studies have been conducted on the treatment of PCD by regulating the intestinal flora, therefore, it is of great significance to explore the alteration of intestinal flora for the therapeutic study of PCD.

2. Mechanisms of PCD

Domestic scholars define PCD as the new appearance of diarrhoea after cholecystectomy, manifested by urgency of defecation, increased frequency of defecation, more than 3 times a day, mostly occurring during the day. The pathogenesis of PCD is very complex, and the current study mainly suggests that the pathogenesis of PCD is closely associated with accelerated colonic motility, impaired intestinal mucosal barrier, and intestinal bacterial flora dysbiosis.

The gallbladder is used to store bile, and cholecystectomy changes the anatomical structure of the gallbladder system, and the physiopathology of bile acids changes accordingly. Hydrophobic bile acids are secreted into the duodenum without stimulation, and goose deoxycholic acid in hydrophobic bile acids can cause diarrhoea by stimulating the cyclic adenosine monophosphate signalling pathway and activating the G-protein-coupled bile acid receptor in the colon to accelerate colonic motility [5]. In addition, after cholecystectomy, bile acid concentration and ratio changes, inducing a decrease in the expression of tight junction proteins ZO-2, JAM-A, AClaudin-3 and Claudin-4, as well as inducing the generation of reactive oxygen species and damage to DNA in the intestinal mucosal epithelial cells, which leads to a weakening of the self-repair ability of the intestinal mucosa, and intestinal mucosa is more susceptible to damage [6], and affects the environment in which intestinal flora can survive. Cholecystectomy (LC) affects the physiology and anatomy of the digestive tract and disrupts the ecological balance of intestinal microorganisms [7]. Bile acids consist of primary bile acids and secondary bile acids. Secondary bile acids are converted from primary bile acids by intestinal microorganisms. Numerous gut bacteria are involved in secondary bile acid production, such as Bifidobacterium and Lactobacillus, both of which solubilise bile acid. A decrease in their numbers will lead to a build-up of primary bile acid, which will increase intestinal osmolality, affect the absorption of water and electrolytes in the lumen of the intestinal cavity, accelerate colonic transit, and increase the frequency and consistency of faecal material, resulting in diarrhoea [8], GI flora play a major role in the pathogenesis of PCD. In addition, high-fat diet and emotional stimulation [9] have significant positive effects on the development of PCD.

3. Changes in Intestinal Flora after Cholecystectomy

Intestinal flora can be broadly classified into three types: commensal, conditionally pathogenic, and pathogenic. In previous studies, it has been observed that cholecystectomy decreases the diversity of intestinal flora, decreasing the number of bifidobacteria, lactic acid bacteria (e.g., Lactobacillus, Lactobacillus), and increasing the number of Escherichia coli and Enterococcus. In recent years, more detailed studies on the intestinal flora of post-cholecystectomy patients have been carried out, mostly by applying 16rRNA gene sequencing, and after statistical analyses of a number of related studies [10-13], it was found

that the abundance of E. faecalis, Prionibacterium spp. which is beneficial to energy metabolic homeostasis, Ruminalococcus spp. and prevotellacopri decreased, and the abundance of Clostridium spp. and the deleterious bacterium Ruminococcus torques increased in abundance.

In order to further investigate the changes of intestinal flora in patients with diarrhoea after cholecystectomy, Li Yandong et al. [14] analysed the faeces of healthy and post-cholecystectomy (PC), PCD and post-cholecystectomy non-diarrhoea (PCND) groups by 16rRNA gene sequencing, and compared the composition, abundance and diversity of intestinal flora of these two groups respectively, and confirmed that there was a decrease of bacterial species in the PCND and PCND groups. A decrease in bacterial species was observed in the PCD group compared to the PCND group, whereas a significant relative abundance of Anaplasma phylum and Proteus was found, whereas a decrease in the relative abundance of Thick-walled phylum and Lactococcus lactis was observed, a significant decrease in the number of Bifidobacteria, and a significant decrease in the abundance of the intestinal microbiota involved in the pathway of lipid metabolism. The most significant results were that Lactobacillus, Citrobacter and Raoultella were significantly positively associated with diarrhoea and Prevotella and Bifidobacterium were significantly negatively associated with diarrhoea.

4. Treatment of PCD based on Changes in Intestinal Flora

4.1 Probiotics and Active Biological Products

4.1.1 Bifidobacteria

Many studies [15-16] have previously demonstrated the effectiveness of Bifidobacteria active biologics in the treatment of diarrhoea. Bifidobacterium triplex capsule is a microecological preparation containing Bifidobacterium bifidum, Enterococcus faecalis and Lactobacillus acidophilus, which is taken orally into the intestinal tract to replenish the beneficial bacteria. It is fixed in the intestinal tract and participates in the construction of the surface flora barrier, supplementing the beneficial flora to promote the restoration of the normal function of the intestinal flora and alleviate the symptoms of diarrhoea. In the study of Liu Qi [17] on 52 PCD patients using Bifidobacterium triplex capsule, its therapeutic efficiency was 96.15% compared to 82.69% in the control group. It was also found that sIgA level was significantly reduced in the experimental group, which indicates that Bifidobacterium triplex capsules play an enhancing role on intestinal immunity. It significantly improved the intestinal flora of patients with postoperative diarrhoea after gallbladder surgery, and had a definite efficacy on PCD. Previously, Menghua Wang [18] also proved in his experiment that the application of Bifidobacterium triplex capsules can enhance the number of beneficial bacteria and inhibit the number of harmful flora, such as Escherichia coli and Enterococcus. Bifidobacterium tetragonum capsules, on the other hand, add Bacillus cereus on top of Bifidobacterium tetragonum capsules, and this bacterium is fixed in the intestines to consume oxygen and promote the growth of beneficial anaerobic bacteria such as Bifidobacterium bifidum. Pan Yanjun et al. [19] applied Bifidobacterium quadruple live capsule to 51 cases of PCD patients for treatment and observation, found that compared with 51 cases of patients receiving conventional treatment, Bifidobacterium quadruple live capsule can increase the number of bifidobacteria such as Bifidobacterium, Lactobacillus, the effective rate of treatment of diarrhoea is 94.12%, which is significantly greater than the control group of 76.47%, and the rate of diarrhoea recurrence of 3.92%, which is less than the rate of diarrhoea recurrence in the control group of 21.57%, regulating the gastrointestinal tract. 21.57%, regulating gastrointestinal hormone levels, which proves that Bifidobacterium bifidum quadruple live bacterial capsule has significant efficacy in treating PCD, and can significantly reduce the recurrence rate of PCD. This is in line with previous studies by Xi Yiping [20] and Liu Hao [21].

4.1.2 Live Bacillus coagulans tablets

Bacillus coagulans has high survival rate, even in high temperature and strong acid environment, so it can pass through strong acid and digestive enzymes [22]. After entering the intestinal tract, it not only provides nutrients for beneficial bacteria, but also creates an acidic and anaerobic environment that promotes the reproduction of beneficial bacteria, and produces coagulin and L-lactic acid that can significantly inhibit a variety of pathogenic bacterial flora, thus helping the intestinal tract to re-establish the ecological balance of the intestinal tract, and treating diarrhoea associated with intestinal flora imbalance. And in a controlled trial for the treatment of post-cholecystectomy diarrhea [23], compared with the use of montelukast group, the addition of Bacillus coagulans tablets group PCD patients intestinal flora more tend to be homeostatic, serum gastrointestinal hormone levels are low, the intestinal mucosal barrier function is more perfect, the rate of adverse reactions is low, and found that the Bacillus coagulans tablets can significantly reduce the chance of number of pathogenic bacteria Escherichia coli, enterococci, and increase the number of beneficial bacterial groups Lactobacillus and Bifidobacterium, improve the intestinal mucosal barrier function and gastrointestinal hormone levels. The effect of Bacillus coagulans tablets in the treatment of post-cholecystectomy diarrhoea has been proved to be excellent. Previously, in the study results of Zhuo Qifeng [24] and Qin Yuling, the therapeutic efficacy of montelukast + Bacillus coagulans tablets was greater than that of montelukast alone. And compared with montelukast, the side effects were lower, yet the therapeutic effect was greatly improved.

However, at present, in the research field of probiotic treatment of PCD, there is no obvious assertion of the possible adverse reactions during its use, and there is no exact standard for the dosage and course of probiotic treatment, which leads to the failure of its experimental data and conclusions to form a complete chain, and the research is still in the primary stage.

4.2 Traditional Chinese Medicine (TCM)

In the system of Chinese medicine, post-cholecystectomy diarrhoea belongs to "diarrhoea ", the patient after surgery, the body of positive qi deficiency, the spleen and stomach transport powerlessness, coupled with the lack of bile viscera, bile excretion is unfavourable, the liver and gallbladder qi,

dampness within the prevalence and lead to diarrhoea. Therefore, the treatment of diarrhoea is based on the legislation of strengthening the spleen and resolving dampness, and the treatment of Chinese medicine stresses "supporting the positive and dispelling the evil", which is similar to the microecology of fostering the beneficial bacterial flora and inhibiting the harmful bacterial flora, and therefore, the application of Chinese medicine to the treatment of PCD is of great significance.

4.2.1 Ginseng and Atractylodes Macrocephalae Powder

Ginseng Ling Atractylodes Macrocephalae strengthens the spleen and strengthens the qi, induces dampness and stops diarrhoea. Pharmacologically, Ginseng & Atractylodes Macrocephalae can regulate gastrointestinal activities in both directions, which can significantly improve the digestive function and reduce the frequency of diarrhoea. In addition, it can also reduce the release of toxins from the intestinal tract, and protect the gastrointestinal mucosa. At present, many studies [25-27] have proved that Ginseng and Atractylodes Macrocephalae can significantly reduce the incidence of PCD, the frequency of diarrhoea, the amount of diarrhoea, and improve the quality of survival of patients. In a controlled study of 110 patients with PCD by Wu Youming et al [25], the treatment efficiency of Ginseng and Baijusan group was 96.7%, and the frequency of diarrhoea and the amount of diarrhoea were reduced compared with the control group. Comparison of the number of intestinal flora in the two groups showed that Ginseng and Baijusan could enhance the number of beneficial bacteria such as Enterococcus, Bifidobacterium and Lactobacillus in the intestinal tract of the patients, and inhibit the number of Escherichia coli, which suggests that Ginseng and Baijusan can regulate the intestinal flora, and has a significant effect on the treatment of PCD. In addition, in a clinical study by Liu Ye [28] and Lan Naixiang [29], Ginseng Ling Baijusan was combined with Bifidobacterium bifidum quadruple vivax tablets, and it was found that the combination of the two medications could shorten the recovery time of the patients while ensuring the safety compared to the two medications used alone.

4.2.2 Ginseng and Spleen Strengthening Soup

Ginseng Strengthening the Spleen Soup strengthens the spleen, benefits the qi, harmonises the stomach and stops diarrhoea. Zhang Zhaohong et al. [30] observed the clinical effect of 36 cases of ginseng spleen-healthy soup combined with Bifidobacterium bifidum tetrapartum tablets in the treatment of post-cholecystectomy diarrhoea, and found that the total effective rate of ginseng spleen-healthy soup group was 94.4%, which was higher than that of Bifidobacterium bifidum tetrapartum capsule alone (80.6%), and the follow-up records showed that the diarrhoea recurrence rate in ginseng spleen-healthy soup group was only 11.8%, which was a significant advantage compared with that of 34.5%. And the addition of ginseng and spleen-healthy soup could affect the number of intestinal flora and significantly reduce inflammatory factors. And in the clinical trial of Cui Qingli [31], the application of bacterial culture and faecal smear found that the ginseng spleen-healthy soup group could reduce the number of Escherichia coli and Enterococcus faecalis, and increase the number of Lactobacillus and Bifidobacterium, and the experimental results suggested that ginseng spleen-healthy pill could reduce the level of serum inflammatory factor, which indicated that it might reduce the recurrence rate of PCD. In conclusion, ginseng spleen-healthy pills can help the intestinal flora to achieve the effect of "supporting the positive and dispelling the evil", and reduce the level of inflammatory factor, which can help PCD patients to achieve the effect of treating and reducing the recurrence rate of PCD.

4.2.3 Umeboshi Pills

As for the TCM pathogenesis of PCD, Professor Lu Weimin believes that "liver wind disturbs the spleen and stomach internally, cold and heat are mixed with deficiency and reality", and Wu Mei Pills use cold and heat together to clear the upper and warm the lower, slow down the liver and regulate the middle, which is in line with the pathogenesis of PCD. Lu Xin [9] used Wu Mei Pills to treat 25 cases of PCD patients and found that its diarrhoea treatment effect was better than that of the western medicine control group, but there was no obvious advantage in the treatment effect of secondary symptoms such as abdominal pain, abdominal distension and poor appetite. In other related studies, it has been confirmed that umeboshi pills help to restore intestinal function, repair the intestinal mucosal barrier, and regulate the intestinal flora, specifically by increasing the number of bifidobacteria and lactobacilli and decreasing the number of Escherichia coli, which may be the relevant mechanism of umeboshi pills in the treatment of PCD. However, the sample size of this clinical study is too small, lack of laboratory evidence, and the follow-up time is too short, so there is a lack of statistical analysis of the recurrence rate, therefore, the therapeutic effect of Umei Pills on PCD still needs to be studied.

In addition to the above formulas, Li Yaling [32] used Xiangsha Liujunzi Tang combined with Siwei San plus and subtractions to treat 37 patients with diarrhoea of liver-depression and spleen-deficiency type after cholecystectomy with an effective rate of 96.88%. In addition, Jianzhi Lishu Fang, Pain and Drainage Essentials Formula, and Sizunzi Tang all have good effects on the treatment of PCD. In clinical practice, the patient should be identified and treated, and the formula should be added and subtracted to achieve the best therapeutic effect.

4.3 Faecal Transplants

Faecal transplantation is an effective means of re-establishing intestinal flora, whereby a faecal suspension from a healthy donor is transplanted into the gastrointestinal tract of a patient, thus helping to restore intestinal flora homeostasis. It has been successfully applied in the treatment of recurrent Clostridium difficile infections [33], and has made significant progress in the treatment of various autoimmune diseases and irritable bowel syndrome. Fujimoto et al. [34] found that faecal transplants can rebuild the intestinal flora of the recipients, affect bile acid metabolism, restore the damaged intestinal mucosa, and restore the normal function of intestinal flora. Cruz-Aguliar et al. [35] showed that faecal transplants can alleviate irritable bowel syndrome. can reduce the degree of abdominal pain in patients with irritable bowel syndrome

without any adverse effects. Guo Ruifang et al [36] found that the number of Lactobacillus and Bifidobacterium intestinalis increased after the patients were treated with FMT. In contrast, the number of Lactobacillus and Bifidobacterium in the intestinal flora of PCD patients decreased, therefore, faecal bacteria transplantation is of great significance for the treatment of PCD. However, the results of many studies on faecal transplants are conflicting and many factors may affect the efficacy of the treatment. Currently, it is controversial whether faecal transplants can be used in the treatment of PCD, and a large number of studies are needed to prove this.

4.4 Low Protein Diet

Diet interacts with intestinal flora and increased abundance of Prevotella improves glucose metabolism [37], and Prevotellacopri (Prevotellaceae) improves cholestasis by enhancing the FXR signalling pathway [38], and adjusting the balance of bile acid metabolism. As mentioned above, the abundance of Prevotella was negatively correlated with the incidence of PCD and the abundance of prevotellacopri decreased after cholecystectomy. Prevotella is a marker of diet, quality of life, and health [37], and the abundance of P. copri was associated with the presentation of a low-protein diet rich in vegetables and fibre [37], and Yi-Yen Liu [39], et al. demonstrated that a high-fibre food could improve bile stasis after cholecystectomy by modulating bile acid metabolism related bacteria to improve intestinal symptoms after cholecystectomy, therefore, a low protein diet is recommended for PCD patients, however, fibre diets may cause bloating and flatulence, therefore the exact mechanism needs to be further explored to further substantiate the therapeutic role of high fibre and low protein diets in PCD patients.

5. Outlook

The incidence of PCD has always been at a high level globally, and therapeutic research on intestinal flora has made significant progress, but there are still problems such as small sample size, lack of standardisation of probiotic dosage and course of treatment, lack of experimental standardised data, and lack of follow-up of recurrence rate. In the process of treating the patients, we should also take into account the age and gender of the patients, the route of the surgery, the diet, and even the emotional factors, and give full play to the advantages of TCM and Chinese medicine to give individualised treatment to the patients with PCD in the course of the clinical diagnosis. In the process of clinical diagnosis and treatment, we should give full play to the advantages of traditional Chinese medicine and individualised treatment for PCD patients.

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