Meta-analysis of Banxia Xiexin Decoction in Treatment of Chronic Cholecystitis

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Abstract: *In order to evaluate the clinical efficacy and safety of Banxia Xiexin decoction in the treatment of chronic cholecystitis, and to provide evidence for the clinical application of Banxia Xiexin decoction. We searched CNKI, VIP, WFPD and CBM databases for clinical randomized controlled trials (RCTS) on Banxia Xiexin decoction in the treatment of chronic cholecystitis. The retrieved literature was screened according to strict inclusion and exclusion criteria. The data were analyzed by using RevMan 5.4.1 software. Resultly, a total of 14 RCTs involving 1127 patients were included, with 566 in the treatment group and 561 in the control group. All the studies reported the total effective rate, 6 studies reported the cure rate, and 3 studies reported the adverse reactions after treatment. Four articles reported the recurrence rate. Three articles reported improvement in abdominal distension and four articles reported improvement in abdominal pain. The results of Meta-analysis showed that the cure rate of Banxia Xiexin decoction in the treatment of chronic cholecystitis was better than the control group (RR=1.66, 95%CI[1.20, 2.30], P=0.002), and the total effective rate was higher than that of the control group (RR=1.23, 95%CI[1.17, 1.29], P<0.00001). Compared with the control group, it had an advantage in preventing disease recurrence (RR=0. 25, 95%CI(0.15, 0.40), P<0.00001). It also improved the symptoms such as abdominal distension (MD=-0.56, 95%CI[-0.87, -0.25], P=0.0004) and abdominal pain (MD=-0.70, 95%CI[-1.21, -0.19], P=0.007). In conclusion, Banxia Xiexin decoction has a good clinical effect on chronic cholecystitis. However, due to the low quality of the included studies, more high-quality randomized double-blind controlled trials are needed to further verify the conclusion, so as to provide more reliable evidence for the treatment of chronic cholecystitis with Banxia Xiexin decoction.*

Keywords: Banxia Xiexin decoction; Chronic cholecystitis; Meta analysis

1. Introduction

Chronic cholecystitis (Chronic Cholecystitis, CC) is a chronic inflammation of the gallbladder. It can be caused by cholecystolithiasis and high-fat diet, or caused by repeated attacks and loss of treatment of acute cholecystitis. The clinical manifestations are recurrent abdomen pain, abdominal distension, belching, greasiness, mild tenderness and percussion pain in the right upper abdomen, and etc [1]. At present, the treatment schemes of western medicine related to CC include diet adjustment, oral drug therapy, surgical treatment and etc [2]. But there are many problems such as adverse reactions, poor curative effect and high recurrence rate. Traditional Chinese medicine treatment provides another choice for the treatment of CC because of its high safety and clinical efficacy. In the theoretical system of traditional Chinese medicine, CC can be attributed to diseases such as "hypochondriac pain" or "gallbladder distention" [3]. The etiology is related to emotional discomfort, improper diet, invasion of external evil, overwork and so on [1]. It can be divided into liver-gallbladder qi stagnation syndrome, liver-gallbladder damp-heat syndrome, qi-blood Stagnation Syndrome, liver spleen deficiency and liver yin insuffficiency syndrome [4]. At present, many studies have shown that Banxia Xiexin decoction has better clinical efficacy than conventional western medicine in the treatment of chronic cholecystitis. However, there is a lack of unified understanding and evaluation of such treatment schemes in the field of traditional Chinese medicine research. There is also a lack of systematic analysis to verify its effectiveness and safety, especially the systematic evaluation of the clinical efficacy of Banxia Xiexin decoction in treating chronic cholecystitis has not been reported yet. Therefore, this study uses the method of Meta analysis to evaluate the clinical efficacy of Banxia Xiexin decoction in the treatment of chronic cholecystitis, in order to provide reference evidence for the application of Banxia Xiexin

decoction in chronic cholecystitis.

2. Materials and methods

2.1. Inclusion criteria

2.1.1. Type of reference

The research method in the literature was randomized controlled trial (RCT).

2.1.2. Subjects

The subjects were patients with chronic cholecystitis and met the basic diagnosis of chronic cholecystitis [2].

2.1.3. Intervention measures

The observation group was treated with Banxia Xiexin decoction as the basic prescription and combined with conventional western medicine. The control group was treated with conventional western medicine.

2.1.4. Outcome indicators

Primary outcome indicators included cure rate and total effective rate. Secondary outcome indicators included recurrence rate, incidence of adverse reactions, improvement of abdominal distension and improvement of abdominal pain.

2.2. Exclusion criteria

(1) literature related to case and expert experience reports, animal trials, reviews and mechanism research was excluded; (2) Literature of clinical research was excluded, intervention measures of which were stored in other incomparable confounding factors, such as the combined application of multiple traditional Chinese medicine preparations, combination of traditional Chinese medicine therapy with acupuncture and moxibustion, acupoint application, etc; (3) Literature with inconsistent diagnostic criteria was excluded; (4) Literature with inconsistent outcome indicators was excluded; (5) Repeated articles and literature were excluded; (6) Literature related to self-control randomized controlled research excluded.

2.3. Literature search

We searched CNKI, VIP, WFPD and CBM databases for clinical randomized controlled trials (RCTS) on Banxia Xiexin decoction in the treatment of chronic cholecystitis. The retrieval time was from the establishment of each database to October 2023. Chinese keywords was "Banxia Xiexin decoction", "Chronic cholecystitis ", "Xie Tong".

2.4. Data extraction

We searched the literature, read the title, the abstract and the key words, then we eliminated literature that did not meet the criteria. In cases of disagreement, a third party was consulted for consensus. And then we extracted the first author, publication year, sample size, random method, intervention measures, course of treatment, outcome index and other contents. After that, we extracted the data of the literature respectively, and finally collated it.

2.5. Quality evaluation of the included literature

The selected RCT literature was evaluated according to the contents of the Cochrane Handbook for Systematic Reviews of Interventions 5.3.0. And the Cochrane Collaboration's tool for assessing risk of bias 2.0 was used to evaluate the literature quality and bias risk. The evaluation contents included selection bias, such as random and allocation hidden methods. It included implementation of bias, such as blind method of researchers and subjects. It included measurement bias, such as blind method of surveyors. It included follow-up bias, such as incomplete report of outcome; reporting bias, such as selective reporting outcomes and other biases. The bias risk of each item was evaluated by high risk, low risk or uncertain risk.

2.6. Statistical Analysis

The data analysis was conducted by using RevMan 5.4.1, employing Relative Risk (RR) and a 95% Confidence Interval (CI) as the resulting statistics. I2 test and Q test were used for the heterogeneity of the literatures. If P > 0.1 and I2 < 50%, the heterogeneity was small and the fixed effect model was utilized for analysis, while the random effect model was used. Forest plots were used to visually represent the analysis findings, whereas funnel plots were utilized to assess potential publication bias.

3. Results

3.1. Literature search results

A total of 179 references were obtained based on the retrieval scheme, and the titles of these references were imported into Medical Literature King V6, by using the software check function. After removing duplicate literature, 79 repetitive literatures were excluded. The article titles and abstracts were reviewed to eliminate irrelevant content, resulting in the exclusion of 64 papers. Further examination of the full text led to the exclusion of an additional 6 papers based on inclusion-exclusion criteria. Finally, a total of 9 papers met all requirements and were included in this study. The retrieval process and results are illustrated in Figure 1.
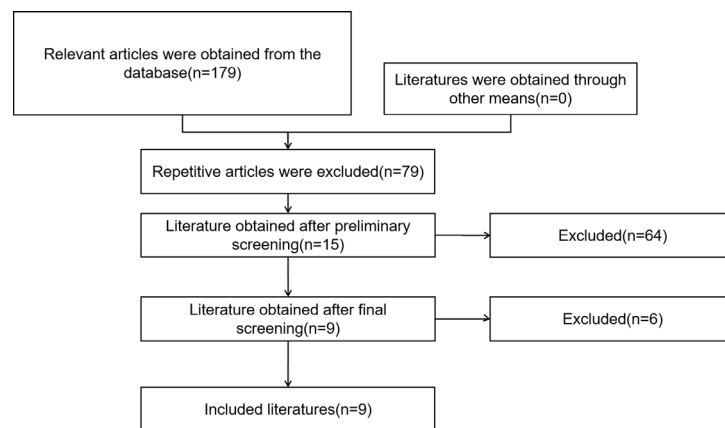

Figure 1: The process of retrieving documents and the resulting graph

3.2. Basic characteristics of included studies

Table 1: Basic characteristics of inclusion study

Reference	Time	Sample Size		Interventions		Course of treatment	Outcome measures
		T	C	T	C		
[5]	2022	40	40	A	Danning tablets	4 weeks	(1)(2)(3)
[6]	2018	43	43	A	B	/	(2)(5)(6)
[7]	2018	57	57	A+B+Antibiotic	B+Antibiotic	15 days	(1)(2)(3)(4)(6)
[8]	2018	48	48	A	B	4 weeks	(1)(2)(4)
[9]	2017	58	58	A+B +Conventional western medicine	B+Conventiol western medicine	8 weeks	(2)(5)(6)
[10]	2014	122	121	A	B+Antibiotic	15 days	(1)(2)(4)
[11]	2010	106	102	A	B+Liangfu pills	2 months	(1)(2)(5)(6)
[12]	2018	45	45	A	Conventional western medicine	10 days	(1)(2)
[13]	2018	47	47	A	Nifedipine	28 days	(2)(3)(4)

Note: T: treatment group; C: control group; A: Banxia Xiexin Decoction; B: Xiaoyan Lidan tablets; Outcome measures: (1) Cure rate; (2) Total effective rate; (3) Incidence of adverse reactions; (4) Recurrence rate; (5) Improvement of abdominal distension; (6) Improvement of abdominal pain.

A total of 9 studies [5-13] were included with a total of 1127 patients, which included the treatment group (n = 566) and the control group (n = 561). The total clinical effective rate was reported in all literatures, the clinical cure rate was reported in 6 articles [5,7,8,10-12], and the adverse reactions after treatment were reported in 3 articles [5,7,13]. The recurrence rate was reported in 4 references [7,8,10,13]. Three articles [6,9,11] reported the improvement of abdominal distension, and four articles [6,7,9,11] reported the improvement of abdominal pain. The basic characteristics included in the study are shown in Table 1.

3.3. Quality evaluation of included documents

The quality of the study was evaluated by the Cochrane Collaboration's tool for assessing risk of bias. The 9 RCTS were mentioned the use of randomly divided into groups, of which 1 literature [13] was grouped by random envelopes in clinical trials. 4 literatures [5,8,10,11] were grouped by random number table method, and the other 4 studies were randomly described but did not mention the specific implementation methods. All studies did not describe the randomized hiding and whether blind or not. Seven literatures [5-11] described inclusion exclusion criteria in detail. All studies mentioned comparable baselines. Two studies [10,11] described the number of shedding cases. The results of bias risk assessment included in the literature are shown in Figure 2.
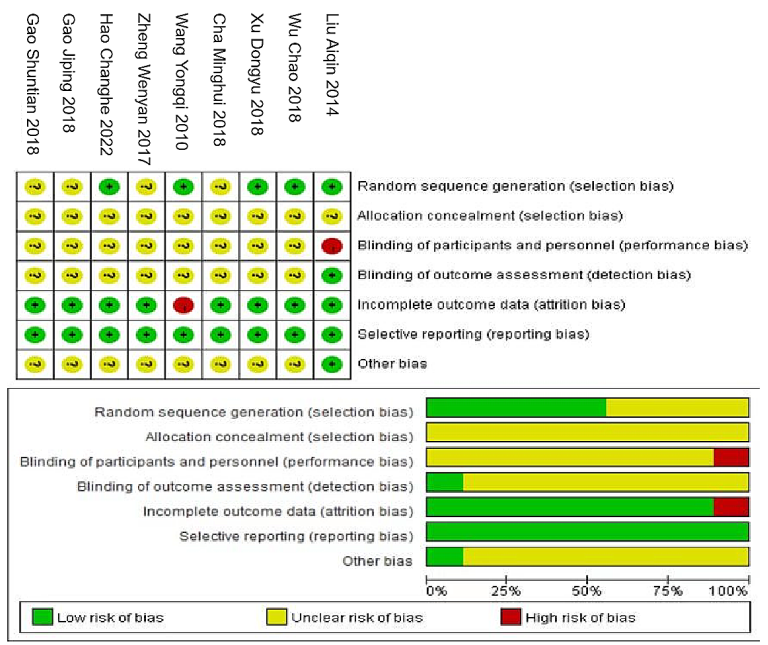

Figure 2: Risk of bias graph

3.4. Outcome index analysis

3.4.1. Cure rate

A total of 6 articles [5,7,8,10-12] reported the clinical cure rate. A total of 418 patients were included in the treatment group, with 205 cured cases. And 413 patients were included in the control group, with 124 cured cases. According to the heterogeneity test: (P=0.01, I2=66%), it indicated high heterogeneity among studies. Therefore, the random effect model was used for analysis. The results of Meta analysis showed that the cure rate of Banxia Xiexin decoction in the treatment of chronic cholecystitis was better than the control group. The difference in the two groups had a statistical significance(RR=1.66, 95%CI[1.20, 2.30], P=0.002). The results are shown in Figure 3.
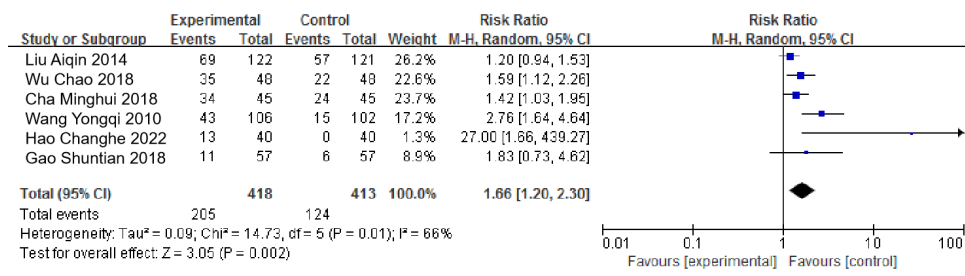
Figure 3: Forest map of cure rate

3.4.2. Total effective rate

A total of 9 articles [5-13] reported the total effective rate. The treatment group included 566 patients with 536 effective cases, while the control group included 561 patients with 432 effective cases. According to the heterogeneity test:(P=0.41, I2=3%), the fixed effect model was used for analysis. The results indicated that the treatment group was superior to the control group in improving the total efficiency. The difference in the two groups had a statistical significance (RR=1.23, 95%CI [1.17, 1.29], P<0.00001). The results are shown in Figure 4.
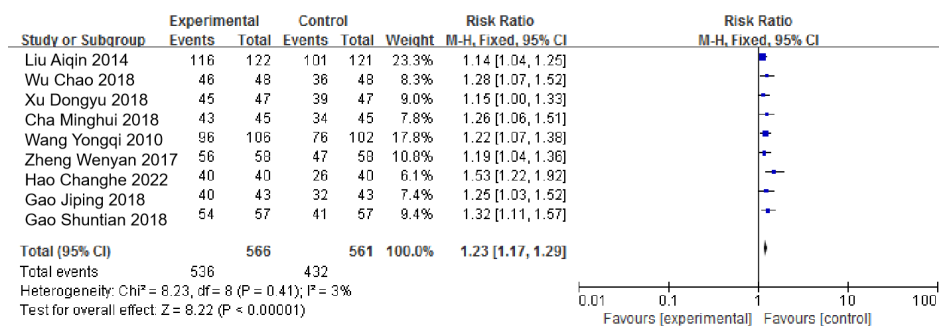

Figure 4: Forest map of total effective rate

3.4.3. Incidence of adverse reactions

A total of 3 articles [5,7,13] reported adverse reactions after treatment, of which 1 study [5] had no adverse events in the treatment group and the control group. 1 study [7] did not specifically report the manifestations of adverse reactions, and other study [13] did not report obvious adverse reactions. There were 2 cases of abdominal discomfort and one patient had a poor appetite in the treatment group. There were 5 cases of abdominal discomfort, 4 patients had a poor appetite, and 1 case of nausea and vomiting in the control group. The number of adverse reactions in the treatment group was less than that in the control group, and the clinical safety was more reliable.

3.4.4. Recurrence rate

The recurrence rate was reported in 4 articles [7,8,10,13], with a total of 547 patients. There were 274 patients in the treatment group, and 18 patients relapsed. In the control group, 73 cases recurred. According to the heterogeneity test:(P=1.00, I²=0%), it indicated small heterogeneity among studies. Therefore, the fixed effect model was used for analysis. The results of Meta-analysis showed that the treatment group had an advantage over the control group in preventing disease recurrence. The difference in the two groups had a statistical significance (RR=0.25, 95%CI[0.15, 0.40], P<0. 00001), The results are shown in Figure 5.
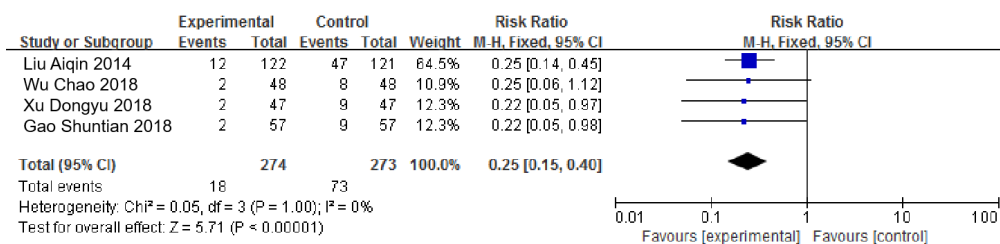

Figure 5: Forest map of recurrence rate

3.4.5. Improvement of abdominal distension

The improvement of abdominal distension was reported in 3 literatures [6,9,11] with a total of 410 patients, including 207 cases in the treatment group and 203 cases in the control group. According to the heterogeneity test, it indicated high heterogeneity among studies. Therefore, the random effect model was used for analysis. The results of Meta-analysis showed that Banxia Xiexin decoction is superior to the control group in improving abdominal distension. The difference in the two groups had a statistical significance (MD=-0.56, 95%CI[-0.87, -0.25], P=0.0004). The results are shown in Figure 6.
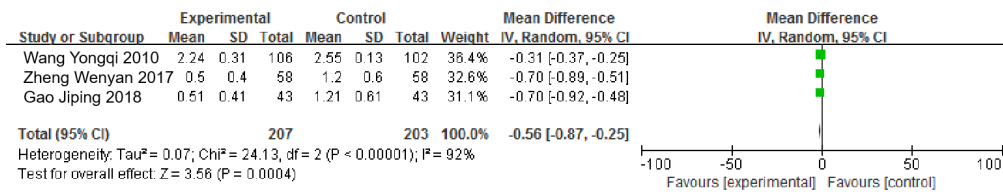

Figure 6: Forest map of abdominal distension improvement

3.4.6. Improvement of abdominal pain

The improvement of abdominal pain was reported in 4 literatures [6,7,9,11]. There were 264 patients in the treatment group and 260 patients in the control group. According to the heterogeneity test, it indicated high heterogeneity among studies. Therefore, the random effect model was used for analysis. The results of Meta analysis showed that Banxia Xiexin decoction can better improve the symptoms of abdominal pain in patients with chronic cholecystitis. The difference in the two groups had a statistical significance(MD=-0. 70, 95%CI[-1.21, -0.19], P=0.007). The results are shown in Figure 7.
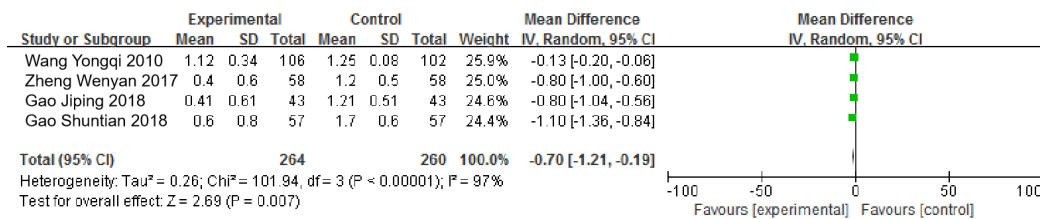

Figure 7: Forest map of abdominal pain improvement

3.4.7. Publication bias analysis

Publication bias analysis was carried out on the total effective rate of Banxia Xiexin decoction in the treatment of chronic cholecystitis [5-13]. The results showed that there was asymmetry in data analysis, indicating that there was a certain degree of publication bias in the total effective rate of the included studies. It may be related to the low sample size of the studies included in the Meta-analysis. (Figure 8)
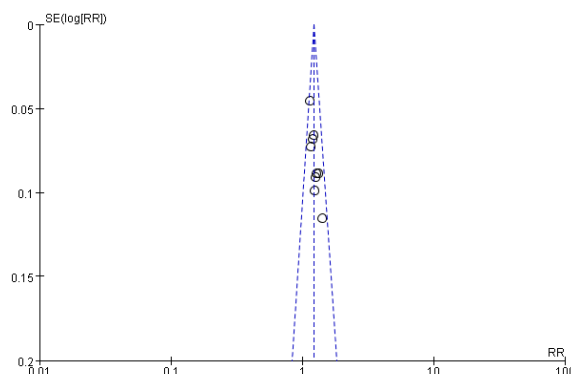

Figure 8: Funnel plot of total effective rate

4. Discussion

Chronic cholecystitis is a common and frequencial disease of the digestive system. Most of the

patients are female, and the ratio of male to female is approximately 1: 1.9 [14]. Studies have found that the prevalence of cholecystitis increases with age [15]. The condition of chronic cholecystitis is prolonged and repeated, and Western medicine mostly uses antibacterial and anti-infective drugs for treatment. It has a long course of treatment and is easy to produce drug resistance, moreover, patients are not susceptible to surgical treatment [16-18]. Traditional Chinese medicine treatment can be based on syndrome differentiation and comprehensive consideration. TCM use more prescription drugs in clinical practice, so the clinical effect is better than the conventional treatment of western medicine [19,20]. Banxia Xiexin Decoction is derived from Shanghan Lun (Treatise on Febrile Diseases). It is composed of Pinellia, Scutellaria baicalensis, Rhizoma coptidis, dried ginger, ginseng, prepared licorice and jujube. Modern pharmacological studies have shown that Pinellia has multi-components, multi-targets and multi-pathways to exert anti-inflammatory and antibacterial effects [21]. Scutellaria baicalensis has a broad spectrum of antibacterial activity, which can eliminate inflammation [22]. Rhizoma coptidis has small toxic and side effects in the treatment of acute and chronic inflammation. And its extract and decoction have good antibacterial effect [23]. Dried ginger has anti-inflammatory effect, and studies have shown that its component 6-gingerol will not cause drug resistance [24]. The flavonoids in licorice have good anti-inflammatory effects [25]. Ginsenoside can inhibit inflammatory factors [26]. Jujube polysaccharide can significantly inhibit pro-inflammatory cytokines in the in vitro antioxidant experiment [27]. Therefore, Banxia Xiexin decoction has certain clinical application value in the treatment of CC through anti-inflammatory and antibacterial effects.

This study conducted a meta-analysis of RCT literature on Banxia Xiexin decoction in the treatment of CC. The results showed that Banxia Xiexin decoction could improve the cure rate and total effective rate of CC. It has more advantages in preventing disease recurrence. At the same time, it can significantly improve the symptoms such as abdominal distension and abdominal pain. Only 3 of the included literatures mentioned adverse reactions. After counting the number of adverse reactions, it was found that Banxia Xiexin decoction was safe and reliable in the treatment of CC. But due to the small sample size, the credibility of the results was low. Publication bias analysis showed that there was asymmetry in data analysis, indicating that there was a certain degree of publication bias in the total effective rate of the included studies.

This study has the following limitations: (1) All the included literatures were in Chinese, and none of them described the concealment scheme, which had the risk of selection bias. Only 5 studies explicitly mentioned the randomization scheme, and only part of the literatures reported the dropout and recurrence. (2) None of the studies included a blank or placebo group as an intervention. (3) Inflammatory factors and imaging indicators were not presented as evaluation indicators. (4) Only 3 studies mentioned adverse events, so the safety of this study could not be better evaluated. According to the analysis of the limitations of this study, this paper puts forward some suggestions for the future research on the treatment of chronic cholecystitis with Banxia Xiexin decoction: (1) The blind method should be used in the formulation of the scheme as much as possible, the selection of random method should be reported in detail, the cases of dropout and recurrence should be recorded in detail, and the long-term follow-up study should be carried out to make the study more objective. (2) Set the control group reasonably. (3) Inflammatory factors and imaging indexes are important criteria for judging the efficacy of chronic cholecystitis, and inflammatory factors and imaging indexes should be increased. (4) The credibility and quality of the study should be improved, and the adverse events of the study should be reported in full detail.

5. Conclusion

In conclusion, Banxia Xiexin decoction has good clinical efficacy in the treatment of chronic cholecystitis, which is worthy of promotion. However, due to the quality limitation of the included studies, the rigor of the conclusions is affected. High-quality randomized double-blind controlled trials are still needed for further verification, and more reasonable clinical recommendations are put forward with better quality research data.

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