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EFFICACY OF MANUAL ACUPUNCTURE ON FUNCTIONAL DYSPEPSIA: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

Xing-xing Yuan[1,§], Bing-yu Wang[1,§], Lei Yang[1], Dan-dan Li[1], Hao Liang[2], Ya-li Zhang[1]

[1]Department of Gastroenterology, Heilongjiang Academy of Traditional Chinese Medicine, No.33 West Dazhi Road, Nangang District, Harbin, Heilongjiang 150001, China; [2]Department of Acupuncture and Moxibustion, Heilongjiang Academy of Traditional Chinese Medicine, No.33 West Dazhi Road, Nangang District, Harbin, Heilongjiang 150001, China. [§] These two authors contributed equally to this work.

Corresponding Author Email: jackieaqi@163.com

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Abstract

Background: This study aimed to systematically review the randomized controlled trials on the efficacy of applying manual acupuncture to functional dyspepsia (FD) compared with conventional gastrointestinal (GI) tract regulator medications.

Methods and Materials: Electronic data bases including the Cochrane Library, PubMed, Embase, Chinese Scientific Journal database (VIP database), China National Knowledge Infrastructure (CKNI), Wan-fang Database and Sino-Med were searched for randomized controlled trials. Utilized data included those published before 30th, Jul. 2016. Manual search on conference abstracts and reference lists was further conducted. Risk of bias evaluation, meta-analysis, sensitivity analysis and all extracted information were performed.

Results: A total of 31 RCTs studies including 2571 participants were identified that include 1314 participants in the groups of manual acupuncture and 1257 participants in the control groups. The result demonstrated that manual acupuncture is more effective in the total effective rate than GI tract regulator medications (OR=3.00, 95%CI [2.33,3.87], $p<0.00001$,). In addition, manual acupuncture also shows a higher excellent rate than GI tract regulator medications (OR=2.51, 95% CI [2.08,3.03], $p<0.00001$). The analysis also showed that manual acupuncture improved symptom scores (WMD=-1.21, 95%CI [-2.13,-0.30], $p=0.009$) and motilin level (WMD=13.99, 95%CI [0.45,27.54], $p=0.04$) of functional dyspepsia significantly compared to GI tract regulator medications. No serious side-effect was observed in both GI tract regulator medications groups and manual acupuncture groups.

Conclusion: The evidence shows that, compared to the GI tract regulator medications, manual acupuncture can significantly improve the total effective rate, excellent rate, symptoms of functional dyspepsia and motilin levels. However, a larger, long-term, rigorous designed trial is necessary.

Keywords: manual acupuncture, functional dyspepsia, meta-analysis, randomized controlled trials

Introduction

Functional dyspepsia (FD) is one of the most prevalent gastrointestinal maladies, which is defined as the presence of any one of the following four cardinal gastrointestinal symptoms according to Rome III criteria diagnosed for functional gastrointestinal disorders, including early satiation, postprandial, epigastric burning and epigastric pain (Tack *et al.,* 2006). In addition, upper abdominal fullness is also considered to be one of the main symptoms of FD in Asia Consensus Report. Although abdominal ultrasonography, upper endoscopy, computed tomography and laboratory examination indicate that patients with FD, without organic or metabolic disease, are still unable to identify the causes of these symptoms (Miwa *et al.,* 2012a).

Considering the definition and diagnostic criterion of FD are different in populations, a variation of the surveyed population and environmental factors, the prevalence of FD is different from country to country (Stanghellini *et al.,* 2016). A global study reports that the total prevalence of FD is 10%-30% worldwide and the prevalence to Rome I criteria is 38%-18% while the prevalence to Rome II criteria is 24%. There is another study shows that the prevalence of functional dyspepsia is 23.8% in the United Kingdom, 15% in the United States and it's 14.7% in North Europe (Mahadeva and Goh, 2006). Several epidemiological studies demonstrate that the prevalence of dyspepsia in Asia is 8%-23%, and 10% in Japan, 20.4% in South Korea (Ghoshal *et al.,* 2011; Makiko *et al.,* 2010; Kim *et al.,* 2014). A study in Singapore shows that the prevalence of FD is 7.9%, while 14.6% rural population and 24.3% urban population suffer from FD in Malaysia (Ho *et al.,* 1998; Mahadeva *et al.,* 2010a; Mahadeva *et al.,* 2010b).

Clinical guidelines for functional gastrointestinal disorders state that prokinetic drugs and proton pump inhibitors are the main choices of FD therapy, however the clinical effect is insufficient and with obvious side effects of long-term medication, the treatment for FD is full of controversy (Ho *et al.,* 2016). Now, more and more patients are eager to substitute complementary and alternative medicine for pharmaceutical medication, especially for herbal medicine and acupuncture therapy, with minimal side effects and significant clinical efficacy (Tillisch., 2007). Acupuncture has been used in China, Japan and South Korea for a long time to treat gastrointestinal diseases, particular in alleviating gastrointestinal symptoms such as abdominal distension, belching, dyspepsodynia and stimulate appetite, with a large amount of experimental and clinical data can be corroborated (Chen *et al.,* 2005; Xu *et al.,* 2006; Lin *et al.,* 2007; Yi *et al.,* 2006; Wang and Yao, 2007). Accompanied by a growing interest in curing FD with acupuncture, it's still necessary to examine the efficacy of manual acupuncture on FD. Our previous study indicate that manual acupuncture can enhance the gastric emptying rate and reduce the symptom scoresin patients with FD, and also improve the status of the depression and anxiety (Yuan *et al.,* 2015). In consideration of limited sample size, the current study is not sufficient to demonstrate the effectiveness of acupuncture. Therefore, we included more RCTs in our analysis of mannual acupuncture in the treatment of FD and the effects of physical therapy such as moxibustion, herbal medicine and electroacupuncture were excluded. In the meantime, the core acupoints and combination of acupoints were also statistical analysised in this article to guide for future research and practice.

Materials and Methods

Data mining

The entry in the following data bases before 30th, Jul. 2016 were searched: Cochrane Library (English), PubMed (English) and Embase (English), Chinese Scientific Journal Database (VIP database, Chinese), China National Knowledge Infrastructure (CKNI, Chinese), Sino-Med (Chinese) and Wan-fang Database (Chinese). MESH terms included "randomized/randomised controlled trials", "functional dyspepsia", "acupuncture", "acupuncture and moxibustion", "manual acupuncture", "needle stimulation", "functional gastrointestinal disorders". In the meantime, manual searching on the reference of reviewed articles, the aspects of conference abstract and reference lists were done independently. EndNote software was used to manage citations obtained in the data bases search.

Case requirement

Studies should meet the following requirements: (1) Research subjects: patients enrolled with an unequivocal diagnosis of FD (including EPS and PDS); blind or allocation concealment was not required; no age, race and gender restrictions; (2) Study design: RCTs studies in both English and Chinese were included; (3) Interventions: needle material, selection of acupoint, acupuncture manipulation, duration of needle retention, duration of course were not further classified in manual acupuncture; pharmacological medication was defined as gastrointestinal tract regulator medications; (4) Outcome measurements: the primary outcome measures included the total effective rate, excellent rate; secondary outcome measures included symptom scores, frequency and amplitude of electrogastrogram, gastric emptying, gastrin (GAS), motilin (MTL) and side effect.

Exclusion

The following cases were not included in this study: (1) Animal experiments, case reports, summaries and reviews; (2) RCTs lacked clear diagnostic criteria or basic information of the subjects or interventions; (3) Manual acupuncture combined with moxibustion, acupoint catgut embedding, acupoint application, acupoint injection, acupoint press, cupping, auricular acupuncture, herbs, music, massage or pharmacological medication; (4) Studies compared with manual acupuncture, moxibustion, acupoint catgut embedding, acupoint application, acupoint injection, acupoint press, cupping, auricular acupuncture or herbs; (5) Studies published repeatedly.

Risk of bias assessment

Based on the criteria of "risk of bias" in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0), assessments included: (1) Selection bias: sequence generation and allocation sequence concealment; (2) Performance bias: blinding of participants and personnel; (3) Detection bias: blinding of outcome assessment; (4) Attrition bias: incomplete outcome data; (5) Reporting bias: selective outcome reporting; (6) Other potential sources of bias. Individual study was described as having an unclear risk of bias, low risk of bias and high risk of bias. Literatures were collected, selected and evaluated by two investigators (B.Y.W and L.Y.). When differences or uncertain of the collected evidence existed, a discussion and analysis were conducted by a third researcher.

Statistical analysis

Review Manager (Version 5.3) was used for meta-analysis and the Stata (Version 12.0) was used for sensitivity analysis. Then, frequency and clustering analysis were conducted by SPSS (Version 19.0). The heterogeneity of the study was analyzed by Cochrane Q test and I^2. The total effective rate, excellent rate of acupuncture on FD were presented as odds ratio (OR), and symptom scores and plasma MTL concentration were expressed as the weighted mean difference (WMD) with 95% confidence intervals (CIs). The fixed effect model proposed by Peto was utilized when the heterogeneity of the test results showed $I2 \leq 50\%$, $P \geq 0.1$; random effect model which proposed by Dersimenian and Laird was used when the heterogeneity test showed $I2 > 50\%$, $P < 0.1$. The funnel plot symmetry analysis was carried out to examine whether there was publication bias when more than ten articles were available for comparison.

Results

Description of selected Trials

Thirty-one trials met our criteria were chosen for the meta-analysis. Figure 1 described the selection procedure in detail, included articles researching and the reason for selection. Table 1 presented a detail description of selected studies.

Risk of bias assessment

Figure 2 described the overall risk of bias and Figure 3 displayed the risk of bias in each study. In the included studies, twelve studies (Tang *et al.*, 2006; Shi *et al.*, 2009; Qin and Guo, 2010; Liu *et al.*, 2011; Jin *et al.*, 2013; Zhang *et al.*, 2014; Zhang *et al.*, 2014; Zhou *et al.*, 2014; Ren *et al.*, 2015; Xu *et al.*, 2015; Yuan *et al.*, 2015; Liu *et al.*, 2016) using random number table and two studies (Liu *et al.*, 2001; Ma *et al.*, 2012) using computer-generated randomization sequence were regarded as low risk of selection bias. Eight studies (Chen *et al.*, 2005; Chen and Kang, 1998; Luo *et al.*, 2002; Li and Li, 2004; Xu and Liu, 2005; Zhao, 2007; Yang *et al.*, 2009; Wu,2010) using visiting sequence rather than randomization were determined as high risk of bias, while the other nine trials (Chen and Gu, 2000; Zhang *et al.*, 2004; Zhao *et al.*, 2005; Sun and Zhang, 2012; Guo, 2013; He, 2013; Shen, 2013; Zhao *et al.*, 2013; Mou., 2015) did not specify the manner of random. Two studies (Liu *et al.*, 2001; Ma *et al.*, 2012) with allocation concealment, one (Liu *et al.*, 2001) using the sealed envelopes, one (Ma *et al.*, 2012) using central telephone and network distribution; only one study (Ma *et al.*, 2012) blindly pick participants and personnel, two studies (Ma *et al.*, 2012; Yuan *et al.*, 2015) carried out blind outcome assessment; thirty-one studies have reported the comparability of baseline, four studies (Ma *et al.*, 2012; Jin *et al.*, 2013; Ren *et al.*, 2015; Liu *et al.*, 2016) reported follow-up, and two studies (Ma *et al.*, 2012; Mou., 2015) with loss of access/exit case reports.

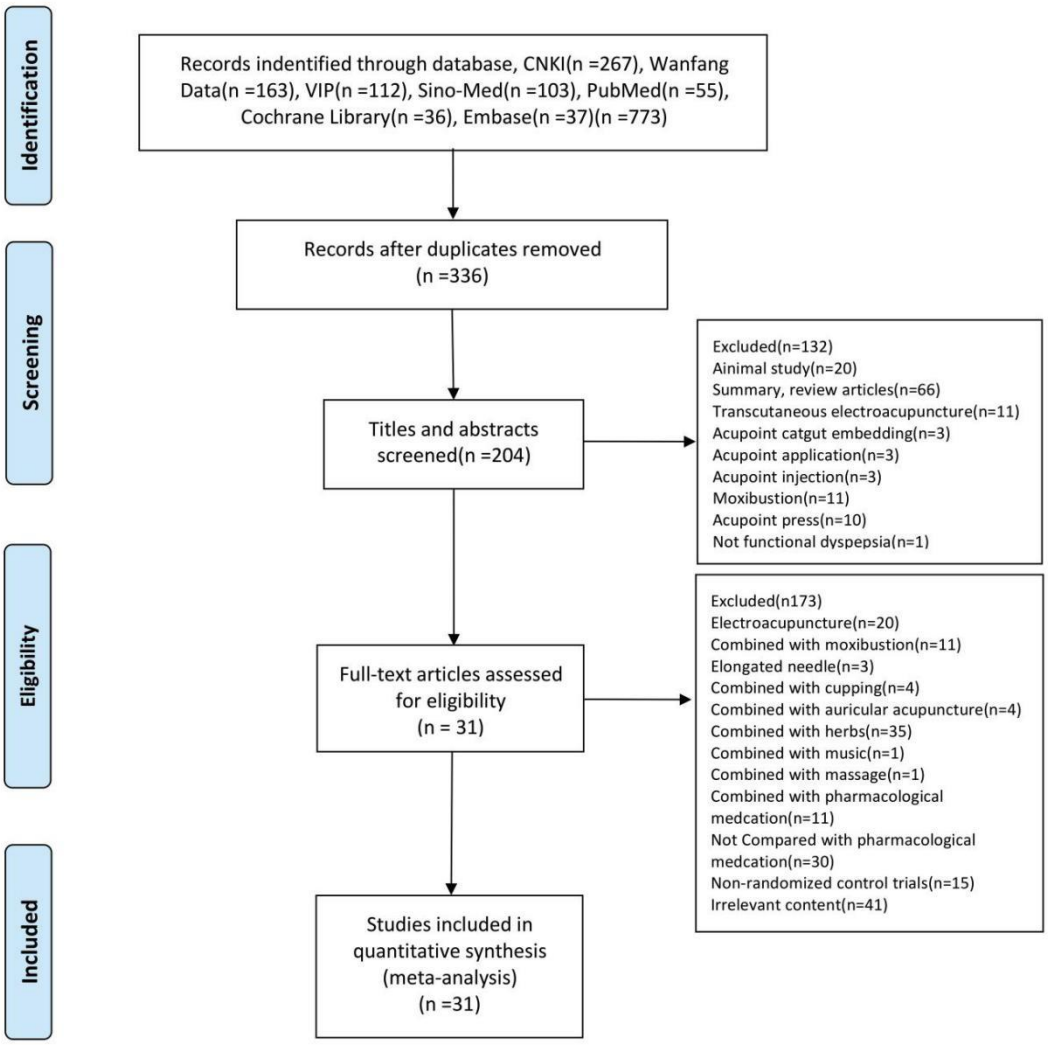

Figure 1: Flow-chat showing selection procedure. RCT: randomization controlled trials. VIP: Chinese Scientific Journal Database; CNKI: China National Knowledge Infrastructure.

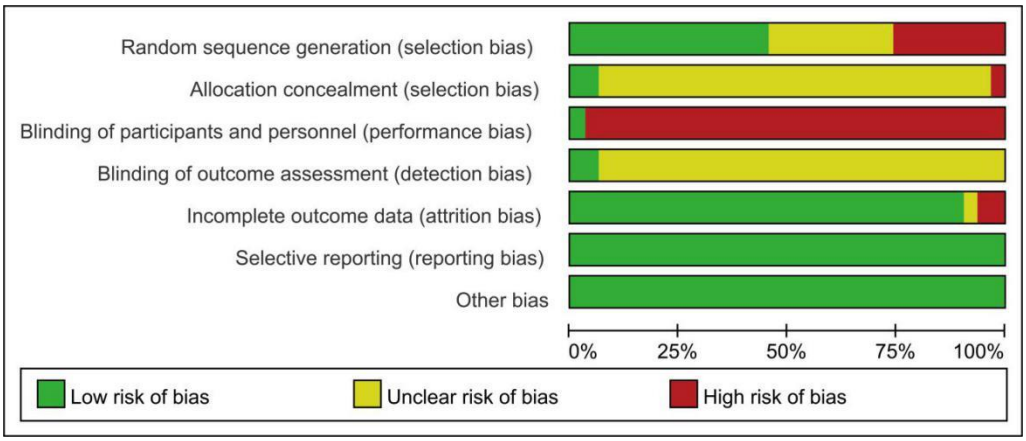

Figure 2: Risk of bias graph

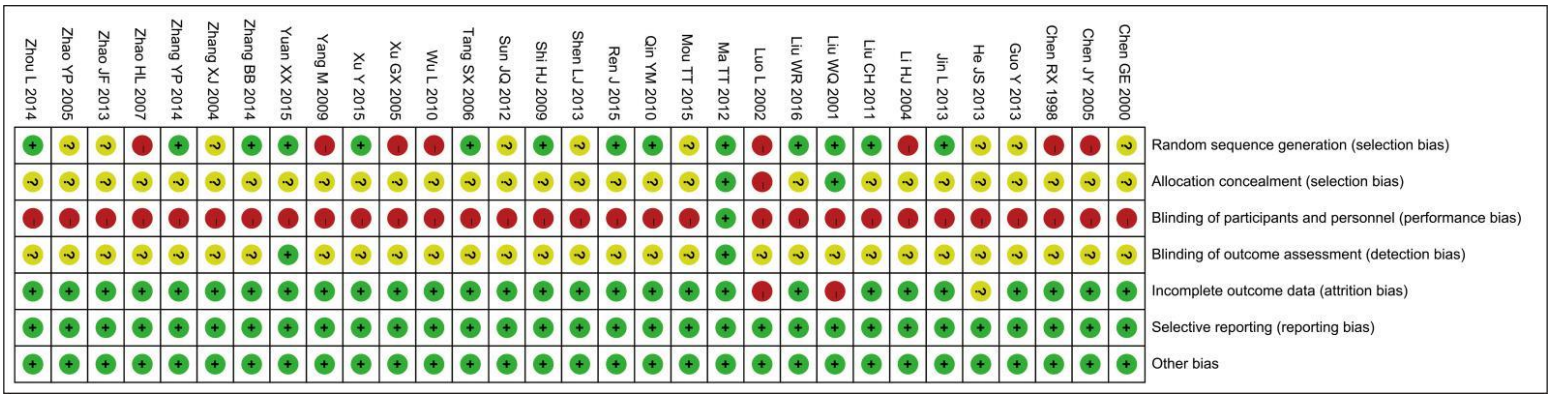

Figure 3: Risk of bias summary

Table 1: Detail and main outcome of selected Studies.

Study ID	Patient（n）		Diagnostic criteria	Interventions		Treatment duration	Main outcomes
	Trial group	Control group		Trial group	Control group		
Chen RX 1998	18	20	Not specified	Acupuncture：Fixed formula	Cisapride	20 days	①②
Chen GE 2000	83	75	Not specified	Acupuncture：Fixed formula	Domperidone	2 weeks	③
Liu WQ 2001	38	30	Not specified	Acupuncture：Fixed formula	Domperidone	1 month	①③⑤
Luo L 2002	40	18	Chicago Conference(Rome I)	Acupuncture：Fixed formula	Cisapride	4 weeks	②③
Li HJ 2004	60	63	Chicago Conference(Rome I)	Acupuncture：Fixed formula	Cisapride	4 weeks	①②③
Zhang XJ 2004	46	46	Rome II	Acupuncture：Fixed formula	Ranitidine+Domperidone	30 d	③
Chen JY 2005	30	30	Rome II	Acupuncture：Fixed formula	Cisapride	1 week	①②⑤
Xu GX 2005	45	42	Chicago Conference(Rome I)	Acupuncture：Fixed formula	Domperidone	30 d	①③
Zhao YP 2005	45	5	Not specified	Acupuncture：Fixed formula	Mosapride	10 d	③
Tang XS 2006	32	30	Rome II	Acupuncture：Fixed formula	Domperidone	30 d	①②③⑤

Zhao HL 2007	50	30	Not specified	Acupuncture: Fixed formula	Domperidone	30 d	③
Shi HJ 2009	45	45	Rome III	Acupuncture: Fixed formula	Cisapride	3 weeks	②③④
Yang M 2009	30	30	Rome III	Acupuncture: Fixed formula	Itopride	14 d	①③
Qin YM 2010	60	60	Rome III	Acupuncture: Fixed formula	Mosapride	6 weeks	②③④⑤
Sun JQ 2012	33	31	Rome III	Acupuncture: Fixed formula	Domperidone	4 weeks	②③
Ma TT 2012	118	119	Rome III	Acupuncture: Fixed formula	Itopride	4 weeks 12 weeks follow-up	②
Guo Y 2013	55	55	Not specified	Acupuncture: Fixed formula	Cisapride	3 weeks	②③④
He JS 2013	24	24	Rome III	Acupuncture: Fixed formula	Domperidone	21d	③
Jin L 2013	36	36	Rome III	Acupuncture: Fixed formula	itopride	12d	②③
Shen LJ 2013	35	35	Rome III	Acupuncture: Fixed formula	Domperidone	2 weeks	②
Zhao JF 2013	40	40	Rome II	Acupuncture: Fixed formula	Domperidone+Omeprazole	2 weeks	②③
Zhang BB2014	33	28	Rome III	Acupuncture: Fixed formula	Mosapride	4 weeks	②③④
Zhang YP 2014	35	35	Rome III	Acupuncture: Fixed formula	Domperidone	20 d	③
Zhou L 2014	36	36	Rome III	Acupuncture: Fixed formula	Itopride	12 d	②③
Mou TT 2015	36	36	Rome III	Acupuncture: Fixed formula	Mosapride	2 weeks	③
Ren J 2015	34	34	Rome III	Acupuncture: Fixed formula	Domperidone	2 weeks	②③

Xu Y 2015	47	46	Guidelines of dyspepsia in China	Acupuncture：Fixed formula	Domperidone	28 d	①②③
Yuan XX 2015	31	32	Rome III	Acupuncture：Fixed formula	Domperidone	30 d	③
Liu WR 2016	34	34	Rome III	Acupuncture：Fixed formula	Domperidone	2 weeks 2 m follow-up	②③

Notes： Chen JY 2005, Yang M 2009, Li ZG 2010, Liu CH 2011, Zhao JF 2013, Zhang BB 2014 had three groups; Qin YM 2010 had four groups and Ma TT 2012 had six groups, but due to the purpose of this research, only two groups were included. ①: EGG: electrogastrogram; ②: Symptom score; ③: Total effective rate; ④: Adverse reactions; ⑤: MLT: Motilin level.

Meta-Analysis Results

A total of thirty-one articles were included in our analysis, 1314 in the trial groups and 1257 in control groups. Patients in the trial groups used the manual acupuncture and the control groups were treated with GI tract regulator medications. Among the control groups, six studies (Chen *et al.,* 2005; Chen and Kang, 1998; Luo *et al.,* 2002; Li and Li, 2004; Shi *et al.,* 2009; Guo., 2013) picked Cisapride, thirteen (Chen and Gu, 2000; Liu *et al.,* 2000; Xu and Liu, 2005; Tang *et al.,* 2006; Zhao., 2007; Sun and Zhang, 2012; He., 2013; Shen., 2013; Zhang *et al.,* 2014; Ren *et al.,* 2015; Xu *et al.,* 2015; Yuan *et al.,* 2015; Liu., 2016) used Domperidone, two studies (Zhang *et al.,* 2004; Wu., 2010) utilized Ranitidine combined with Domperidone; four studies (Zhao *et al.,* 2005; Qin and Guo, 2010; Zhang *et al.,* 2014; Mou., 2015) treated with Mosapride, four studies (Yang *et al.,* 2009; Ma *et al.,* 2012; Jin *et al.,* 2013; Zhou *et al.,* 2014) with Itopride, one study (Liu *et al.,* 2011) used Clebopride and one (Zhao *et al.,* 2013) utilized Omeprazole together with Mosapride. Three studies (Luo *et al.,* 2002; Li and Li, 2004; Xu and Liu, 2005) used the Rome I diagnostic criteria, four studies (Chen *et al.,* 2005; Zhang *et al.,* 2004; Tang *et al.,* 2006; Zhao *et al.,* 2013) utilized the diagnostic criteria of Rome II, seventeen studies (Shi *et al.,* 2009; Yang *et al.,* 2009; Qin *et al.,* 2010; Wu., 2010; Liu *et al.,* 2011; Sun and Zhang, 2012; Ma *et al.,* 2012; He., 2013; Jin *et al.,* 2013; Shen., 2013; Zhang *et al.,* 2014; Zhang *et al.,* 2014; Zhou *et al.,* 2014; Mou., 2015; Ren *et al.,* 2015; Yuan *et al.,* 2015; Liu., 2016) adopted the criteria of Rome III and one (Xu *et al.,* 2015) used the Chinese diagnostic criteria, the remaining six (Chen and Kang, 1998; Chen and Gu, 2000; Liu *et al.,* 2001; Zhao *et al.,* 2005; Zhao., 2007; Guo., 2013), criteria were not reported.

Analysis of total effective rate

The total effective rate in twenty-seven RCTs with 2168 patients were listed (Chen and Gu, 2000; Liu *et al.,* 2001; Luo *et al.,* 2002; Li *et al.,* 2004; Zhang *et al.,* 2004; Xu *et al.,* 2005; Zhao *et al.,* 2005; Tang *et al.,* 2006; Zhao., 2007; Shi *et al.,* 2009; Yang *et al.,* 2009; Qin *et al.,* 2010; Wu., 2010; Liu *et al.,* 2011; Sun and Zhang, 2012; Guo., 2013; He., 2013; Jin *et al.,* 2013; Zhao *et al.,* 2013; Zhang *et al.,* 2014; Zhang and Zhang, 2014; Zhou *et al.,* 2014; Mou., 2015; Ren *et al.,* 2015; Xu *et al.,* 2015; Yuan *et al.,* 2015; Liu., 2016). Heterogeneity result shown that I^2=9%, so a fixed-effect model was applied in this statistical analysis. In general, the total effective rate of manual acupuncture was greater than the efficacy of GI tract regulator medications (P＜0.00001, OR=3.00, 95%CI [2.33,3.87]). (Figure 4). The funnel plot analysis shown that there was no obvious publication bias. (Figure 5).

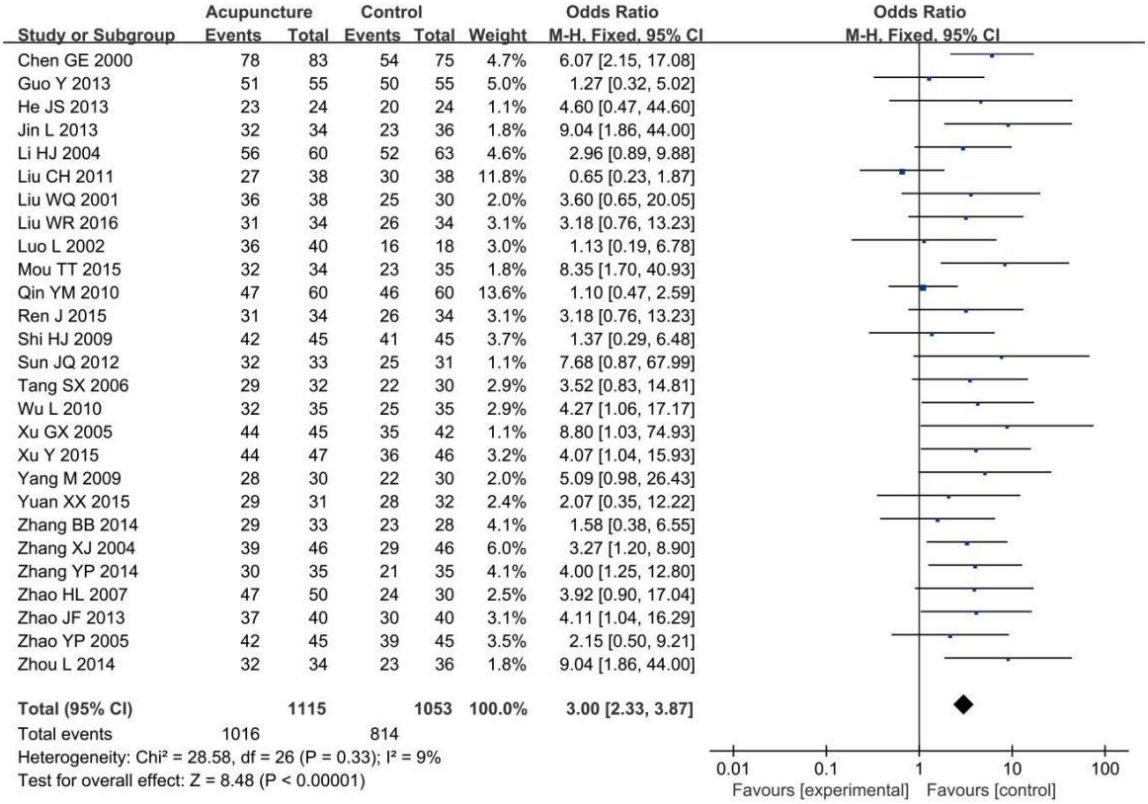

Figure 4: Forest plot of total effective rate of FD

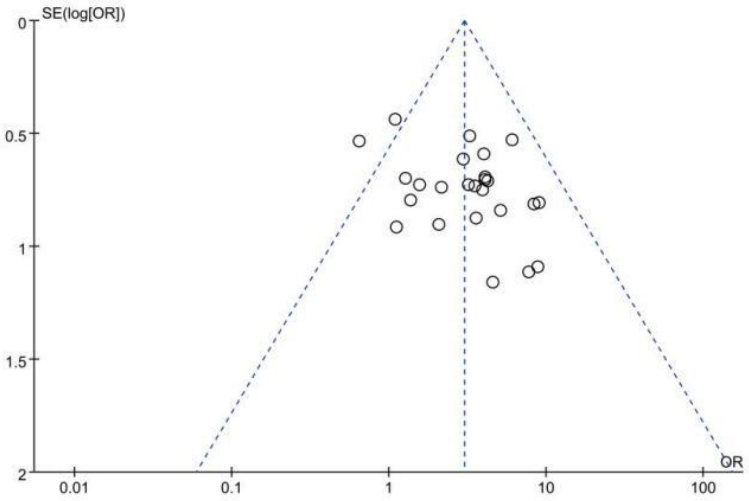

Figure 5: Funnel plot of total effective rate of FD

Analysis of excellent rate

Heterogeneity shown I^2=26%, so a fixed-effect model was conducted in this analysis. The excellent rate of manual acupuncture suggested a significant difference compared with GI tract regulator medications (P＜0.00001, OR=2.51, 95%CI [2.08,3.03]). (Figure 6).

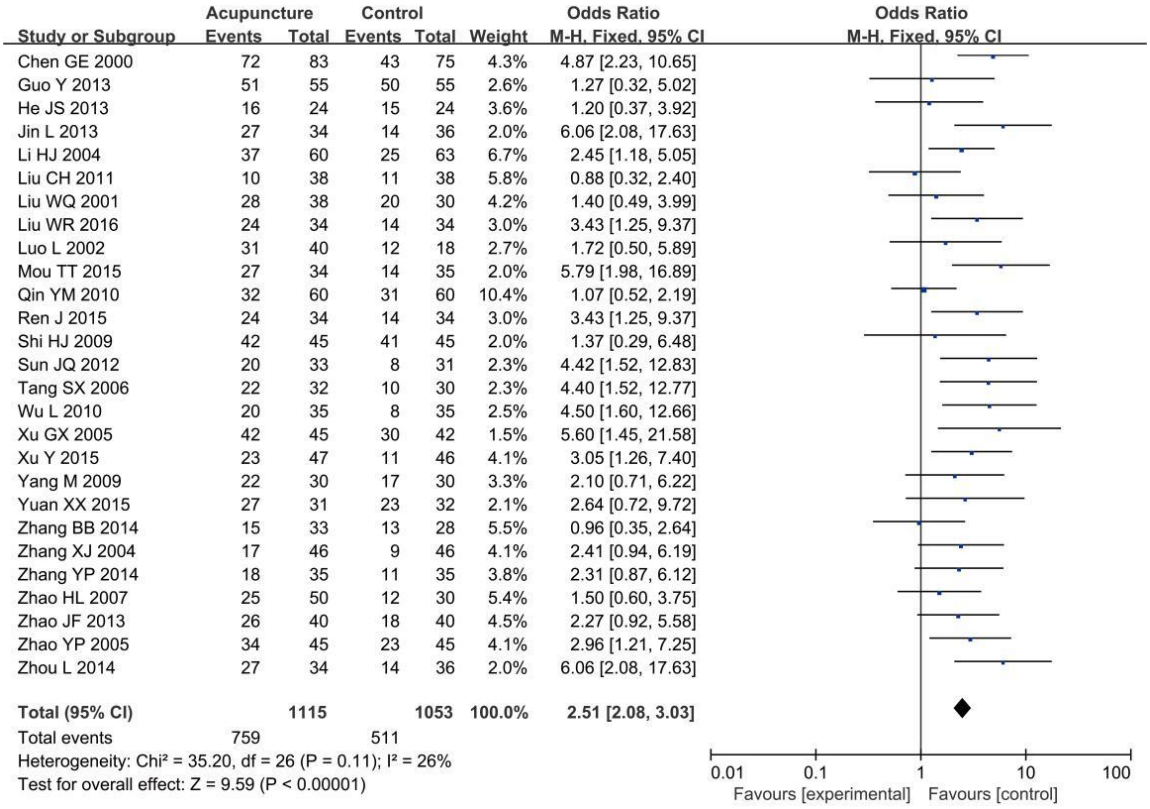

Figure 6: Forest plot of the excellent rate of FD

Analysis of symptom scores

Thirteen studies contributed to the analysis of symptom scores of FD, with 967 patients contribute to the outcome data (Chen *et al.*, 2005; Chen and Kang, 1998; Li and Li, 2004; Tang *et al.*, 2006; Qin *et al.*, 2010; Sun and Zhang, 2012; Jin *et al.*, 2013; Shen., 2013; Zhang *et al.*, 2014; Zhou *et al.*, 2014; Ren *et al.*, 2015; Xu *et al.*, 2015; Liu *et al.*, 2016). The data were analyzed by random-effect model due to the significant heterogeneity (P＜0.00001, I^2=90%). Manual acupuncture showed a significant improvement in symptom scores compared to GI tract regulator medications (P=0.009, WMD=-1.21, 95%CI [-2.13, -0.30]) (Figure 7).

Because of the significant heterogeneity, a sensitivity analysis was performed. The sensitivity analysis indicated that the elimination of any trial did not significantly change the results in homogenization or CIs, meaning that the result is reliable. (Figure 8).

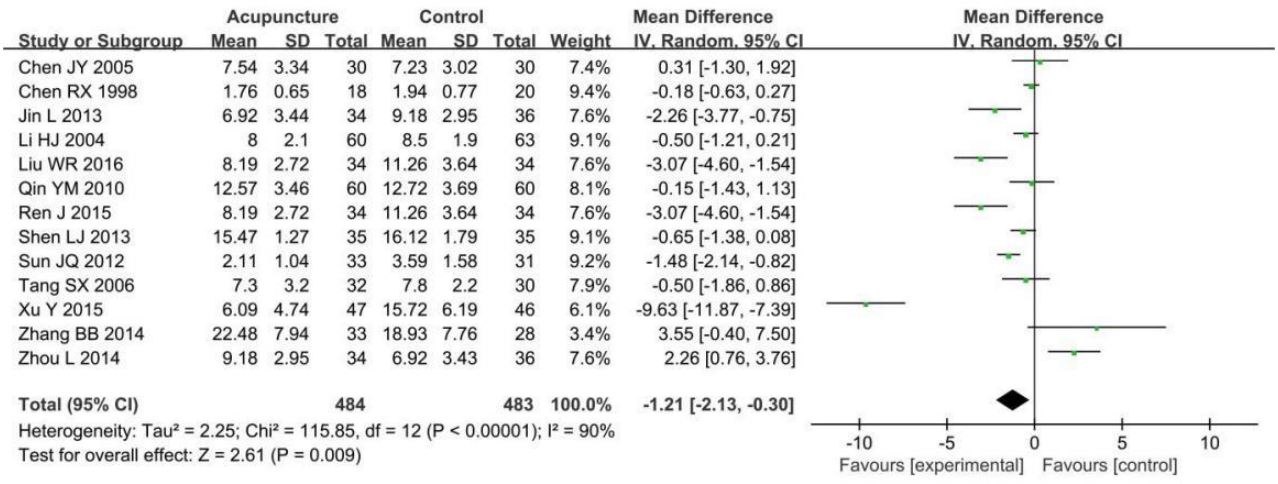

Figure 7: Forest plot of the symptom score of FD

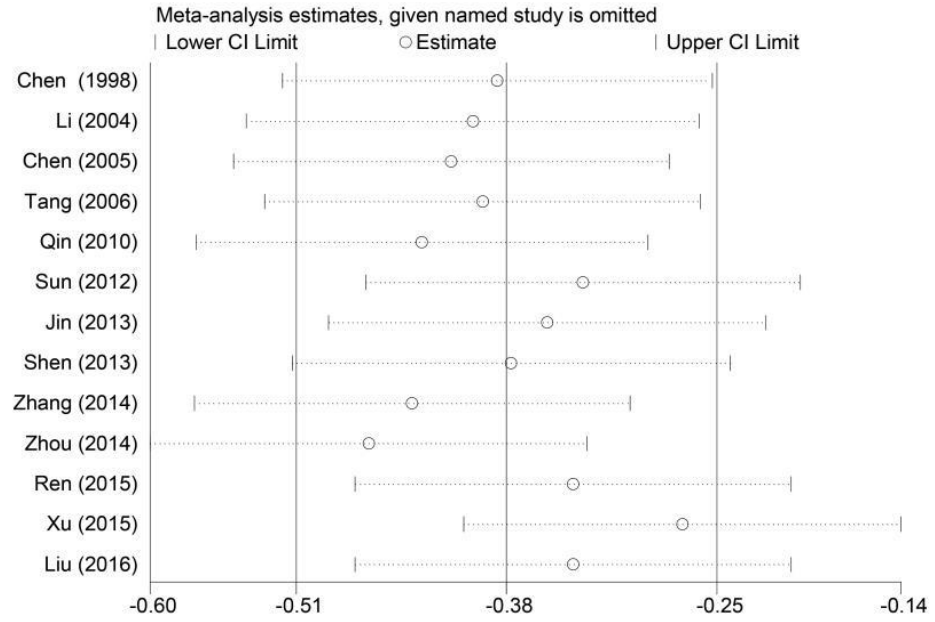

Figure 8: Sensitivity analysis of trials contributing to the symptom score of FD

Analysis of motilin level

MTL was measured as a follow-up outcome in four studies (Chen *et al.*, 2005; Liu *et al.*, 2001; Tang *et al.*, 2006; Qin *et al.*, 2010). The data were analyzed using a fixed-effect model according to the test of heterogeneity (P=0.55, I2=0%). Manual acupuncture showed a significant improvement in MTL compared to GI tract regulator medications (P=0.04, WMD=13.99, 95%CI [0.45,27.54]) (Figure 9).

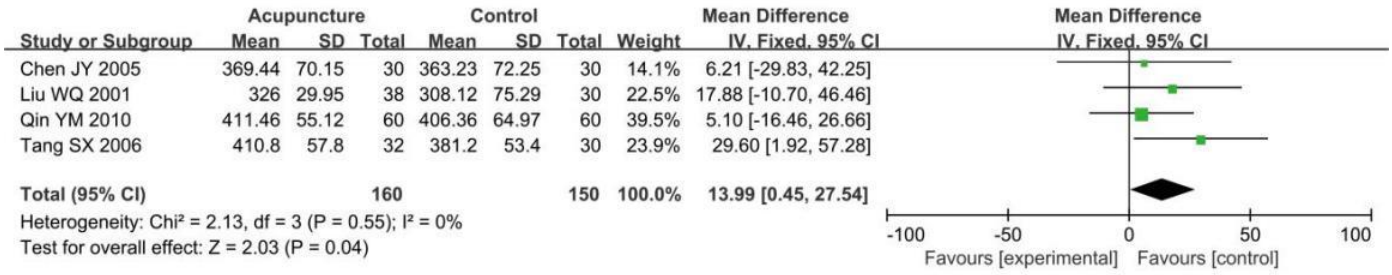

Figure 9: Forest plot of the motilin of FD

Frequency analysis of acupoint

Frequency analysis was performed on acupuncture prescriptions included in the study，a total of 43 acupoints were involved. Among these, ST35, P6, CV12, ST25, LR3, BL21,, BL2, CV6, LR14 and CV10 were the most frequently used acupoints (table 2).

Table 2: Frequency analysis of acupoints in treatment of FD

	Acupoint	Frequency	Percentage	Cumulative percentage		Acupoint	Frequency	Percentage	Cumulative percentage
1	ST36	57	9.4	44.0	23	SP9	4	.7	.7
2	P6	51	8.4	52.4	24	ST34	4	.7	.7
3	CV12	46	7.6	60.0	25	BL17	3	.5	.5
4	ST25	26	4.3	64.3	26	GB34	3	.5	.5
5	LR3	19	3.1	67.4	27	ST40	3	.5	.5
6	BL21	18	3.0	70.4	28	CV17	2	.3	.3
7	BL20	16	2.6	73.1	29	LI4	2	.3	.3
8	CV6	16	2.6	75.7	30	ST37	2	.3	.3
9	LR14	14	2.3	78.0	31	ST39	2	.3	.3
10	CV10	10	1.7	79.7	32	ST42	2	.3	.3
11	GV20	10	1.7	81.3	33	BL23	1	.2	.2
12	CV13	9	1.5	82.8	34	BL25	1	.2	.2
13	EX-HN 3	9	1.5	84.3	35	CV14	1	.2	.2
14	BL18	8	1.3	85.6	36	CV3	1	.2	.2
15	SP4	8	1.3	86.9	37	EX-HN 1	1	.2	.2
16	SP6	8	1.3	88.3	38	HT5	1	.2	.2
17	ST44	7	1.2	89.4	39	HT7	1	.2	.2
18	CV4	6	1.0	90.4	40	KI6	1	.2	.2
19	LR2	6	1.0	91.4	41	LU7	1	.2	.2
20	GV24	5	.8	92.2	42	SJ5	1	.2	.2
21	LR13	5	.8	93.1	43	SP15	1	.2	.2
22	BL15	4	.7	93.7	Total		605	100.0	100.0

Cluster analysis of acupoints Dendrogram revealed that the main points group including: ST36, P6, CV12；ST25, BL20, BL21；LR14, LR2, BL18, LR3；SP9，ST44. (Figure 10).

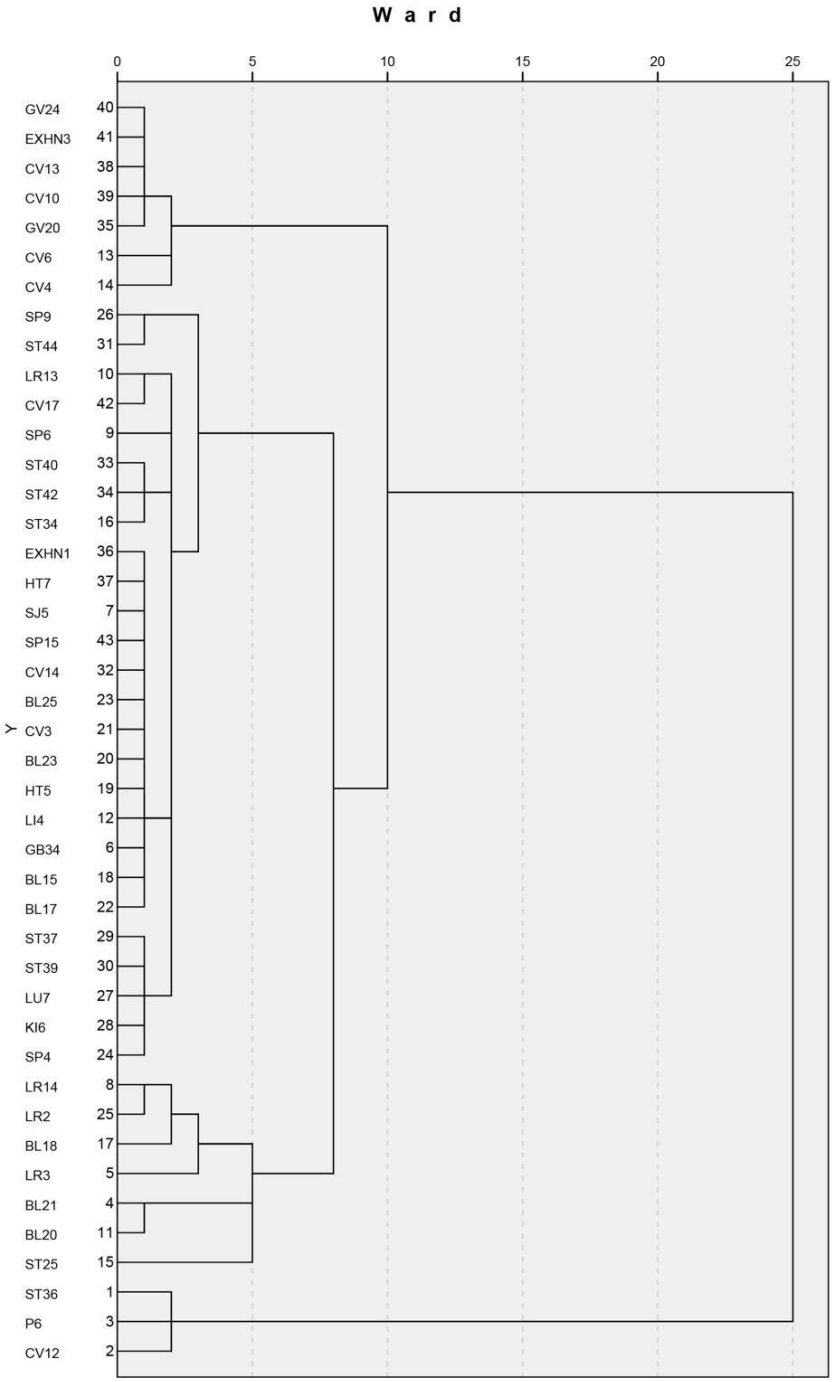

Figure 10: Dendrogram of acupoint for FD

Adverse events

Adverse events were presented in eight trials (Shi *et al.*, 2009; Qin *et al.*, 2010; Liu *et al.*, 2011; Sun and Zhang, 2012; Ma *et al.*, 2012; Guo., 2013; Jin *et al.*, 2013; Zhang *et al.*, 2014). Three trials (Shi *et al.*, 2009; Ma *et al.*, 2012; Guo., 2013) reported a subcutaneous hematoma after acupuncture, three trials (Shi *et al.*, 2009; Liu *et al.*, 2011; Sun and Zhang, 2012) reported dizziness and headache, mild diarrhea were observed in three trials (Shi *et al.*, 2009; Qin *et al.*, 2010; Sun and Zhang, 2012) of the control group. All these reactions were quickly disappeared after termination of the treatment. No serious adverse event was recorded.

Discussion

FD is one of the most frequently gastrointestinal disorders encountered by the digestive outpatient physician; however, the pathological mechanism of FD is still unclear. Evidence shows that numerous factors were involved in the occurrence of the disease, including visceral hypersensitivity, gastric motility abnormalities, social psychological factors, Helicobacter pylori infection, environmental factor, genetic disorder, lifestyle and diet habits. Among them, gastric motility abnormalities and visceral hypersensitivity were considered to be the main factors, while it's also believed that these factors are complex and mutual influencing (Miwa *et al.,* 2012b; Lee *et al.,* 2004; Miwa *et al.,* 2011; Mimidis *et al.,* 2008; Tack and Lee, 2005). Owing to the unclear pathophysiology, it is not surprising that the current limitation of therapy for FD. Complementary and alternative medicine, including acupuncture and moxibustion have attracted the attention of both practitioners and patients (Ouyang and Chen, 2004).

Acupuncture can treat a variety of disease. It is being gradually accepted and valued by western countries. In fact, this approach has been used in the treatment for functional gastrointestinal disorders in China for many years (Zheng *et al.,* 2009). It has been found that acupuncture can significantly improve dyspepsia gastric emptying function, decrease the symptom score, and enhance the quality of life and mental status (Xu *et al.,* 2006; Zeng *et al.,* 2015a; Zeng *et al.,* 2012; Park *et al.,* 2009; Zeng *et al.,* 2015b). The mechanism may be the brain responses elicited by stimulation of acupuncture, or the body metabolism, that is associated with increasing gastrin in gastric, slowing wave frequency and the propagation velocity (Jin *et al.,* 2015; Li *et al.,* 2014; Wu *et al.,* 2010).

There have been several articles on the meta-analysis of the acupuncture treatment for FD. One article reported that there was no significant difference between domperidone and manual acupuncture in improving symptom scores (RR: 1.24, 95%CI[0.97, 1.58]) (Tang *et al.,* 2006). However, the results of this systematic review shown that manual acupuncture was superior to GI tract regulator medications on total effective rate (OR = 3.00,95%CI, [2.33,3.87]) and excellent rate (OR = 2.51,95%CI [2.08,3.03]]). More than this, manual acupuncture was more effective in improving functional dyspepsia scores than GI (WMD=-1.21,95%CI, [-2.13, -0.30]). Our results also showed that MTL improved significantly in the manual acupuncture group compared with GI tract regulator medications (WMD = -13.99,95%CI, [0.45,27.54]), which was contrary to the result of Zhou in which manual acupuncture failed to elevate the concentration of plasma MTL (SMD: 0.67, 95%CI:[-0.07, 1.42]) (Zhou WM *et al.,* 2016). In addition, we also performed frequency analysis and cluster analysis on 60 acupuncture prescriptions of 31 RCTs, the results showed that ST35, P6, CV12, ST25, LR3, BL21,, BL2, CV6, LR14 and CV10 were the most frequently used acupoints, and ST36, P6, CV12； ST25, BL20, BL21； LR14, LR2, BL18, LR3； SP9， ST44 were the main acupoints groups treating for FD.

Although our results confirm the effectiveness of mannual acupuncture, there are still multiple factors that did not escape our attention.Firstly the methodological quality of the including literatures, eight articles (25.8%) had a high risk of bias and randomization procedures were unclear in nine studies (29.0%). Only two trials (6.5%) reported methods with an allocable sequence. Although all studies had reported the comparability of the baseline, there was only one study (3.2%) blindly pick participants and personnel. Two trials (6.5%) carried out a blind survey on outcome assessment. Secondly, another unavoidable reason which led to the collection bias was that all selected literatures were retrieved in Chinese and English databases, no other language databases were searched. In addition, regardless of the fact that two of them were published in English, all the studies were from China. One could anticipate that there was unpublished literature, contributing to the bias. Thirdly, there was a significant heterogeneity in the analysis of the symptom scores of FD ($P < 0.00001$, I2=90%). For this reason, we carried out the sensitivity analysis to explore the sources of heterogeneity. Unfortunately, we could not obviously change CIs or led to homogenization while cut off anyone trial. So the heterogeneity was still not obvious. In conclusion, the low affirmation of the inclusion could lead to significant heterogeneity, high risk and bias, which seriously affected the reliability of the evidence. Therefore, our conclusion should be cautious.

Conclusion

Acupuncture has promising efficacy in the treatment for functional dyspepsia, compared to the standard medical treatment, it has a better clinical efficacy. Acupuncture is also a safe method to improve the symptom scores and MTL level. However, determining how to deliberate acupuncture deserves further studies.

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