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ORIGINAL

EFFECTS OF ACUPUNCTURE AND 5-HT3 RECEPTOR ANTAGONISTS ON MAINTAINING PHYSICAL ACTIVITY IN ATHLETES UNDERGOING CHEMOTHERAPY FOR CINV

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ABSTRACT

Objective: To evaluate the therapeutic effects and the commonly used acupoint selection scheme of acupuncture combined with anti-emetic drugs on CINV after chemotherapy in athletic patients. **Methods:** a systematic review of the existing randomized controlled trials of acupuncture combined with western medicine in the treatment of vomiting and hiccup in athletic patients after chemotherapy. The meta-analysis was conducted by Revman 5.3 software. **Results:** a total of 13 related literatures were included in this study, including 824 athletic patients with nausea and vomiting after chemotherapy, including 413 cases in the observation group and 411 cases in the control group. Meta analysis showed that the total effective rate of the observation group was higher than that of the control group [RR=1.27,95%CI (1.18, 1.37), P<0.00001]. **Conclusion:** Compared with conventional treatments, acupuncture combined with western medicine can improve the curative effect on vomiting and hiccup symptoms of tumor patients after chemotherapy, but due to the limitations of the number and quality of included studies, the above conclusions need to be verified by more high-quality studies.

KEYWORDS: acupuncture; 5-HT3 receptor antagonist; CINV;Tumor chemotherapy

1. INTRODUCTION

With the increasing incidence of cancer year by year, its treatment has become a hot issue in the forefront of medical research. According to the statistical data report of the China Cancer Center in 2019, cancer is currently one of the first causes of death for the elderly and residents in China, and the incidence and mortality of cancer in China are increasing year by year. It is estimated that the number of deaths caused by cancer in China will reach more than 12 million from 2019 to 2030 (Li et al., 2019). Chemotherapy can effectively inhibit the continuous proliferation of malignant tumors by using the interaction of anticancer chemicals, prolong the survival period of athletic patients and athletic patients, and is an effective treatment method for malignant tumors.

However, the use of chemotherapy drugs can also cause many adverse reactions in the body (Soares Costa et al., 2022). Researchers have found that the stimulation of nerve center and gastrointestinal digestive system will cause some digestive system reactions, such as nausea and vomiting, hiccup, constipation and other symptoms, while nausea and vomiting are considered as a gastrointestinal reaction that directly affects the quality of life of chemotherapy athletic patients (XJ Zhang & Zhang, 2006). The symptoms of nausea and vomiting in the course of chemotherapy drug treatment are collectively referred to as chemotherapy-induced nausea and vomiting (CINV). This symptom may lead to the loss of body fluid and dehydration shock in athletic patients, and also seriously affect the psychological status of athletic patients, thus reducing the efficacy of chemotherapy. At present, the main western medicine treatment for CINV is the use of 5-HT3 receptor antagonists such as ondansetron and granisetron, but it has its own limitations because it is easy to produce drug resistance and does not have continuous ideal effect (Y. Chen, 2015). Nowadays, acupuncture and moxibustion as a therapeutic method has been applied to the treatment of clinical gastrointestinal diseases, and has been confirmed by many studies (Yang, Zhang, & Li, 2019).

In addition, the combination of acupuncture and moxibustion and Western medicine for the treatment of CINV in athletic patients after chemotherapy has gradually been valued and recognized by clinicians because of its quick effect, convenient operation, and low side effects. However, there is still a lack of reliable evidence-based medical evidence and standardized clinical procedures. This study intends to conduct a meta-analysis of the existing domestic and foreign clinical randomized controlled studies of acupuncture and moxibustion combined with western medicine in the treatment of CINV, and sort out the commonly used acupuncture and moxibustion point selection schemes, to clarify the improvement of the efficacy of acupuncture and moxibustion combined with western medicine on CINV and the acupuncture and moxibustion treatment scheme.

2. Data and methods

2.1 Inclusion criteria

(1) Research field: clinical randomized controlled clinical research, limited to Chinese and English. (2) Study object: The study object is a confirmed tumor patient who meets the requirements of chemotherapy. The patient's age, sex, course of disease, tumor location, pathological source, etc. are not limited. (3) Intervention measures: treatment measures: observation group: acupuncture and moxibustion (including ordinary acupuncture, warm acupuncture and moxibustion, electroacupuncture, acupoint application) combined with conventional western medicine; Control measures: routine treatment with western medicine (application of 5-HT3 drugs). (4) Outcome indicators:

2.2 Exclusion criteria

(1) No randomized controlled trial was set; (2) The reported data is incomplete; (3) The results were not analyzed effectively (4) there were obvious data errors (5) the test setup and other literature could not be combined for analysis (6) the literature records were incomplete

2.3 Literature retrieval

The Chinese database is the full text database of Chinese journals, the database of CNKI,Wangfang、VIP. The English database is the database of PubMed 、Cochrane、Medline 及 Embase SinoMed. The retrieval date is December 2021. Chinese subject search keywords are "chemotherapy", "tumor chemotherapy", "vomiting", "gastrointestinal reaction", "acupuncture and moxibustion", "acupuncture", "electroacupuncture" points "," ear acupuncture ", etc; The English search terms are "Chemotherapy" and "tumor chemistry" and "vocalizing" and "gastrointestinal reaction" and "acupunture", "moxibustion" and "electro-acupunture", "points" and "ear acupunture".

2.4 Literature screening and quality evaluation

The selection, collection and quality evaluation of documents are conducted by two professional personnel respectively. In case of disagreement, they discuss with each other and reach a consensus.

(1) The classification data of relevant documents obtained in the search of this article are accurately screened: first, all duplicate classified documents are eliminated; Secondly, read the article title and the abstract of the original text of this article, and eliminate the literature that is insufficient and can be clearly included in the exclusion criteria of this article; Finally, after carefully reading the full text of the article, the data were comprehensively eliminated

according to the exclusion method of comprehensive scientific analysis standard, and all qualified documents included in the comprehensive analysis standard of scientific evaluation were obtained. (2) Basic data and data extraction of the included literature include the first author, publication time, sample size, grouping setting, course of treatment, intervention measures, and outcome indicators (3) The literature quality risk assessment required for the clinical literature included in each research project: two clinical research staff independently carried out the literature quality prediction and evaluation according to the research results bias and risk evaluation tool requirements of the clinical randomized control table in the project of the Technical Specifications for Clinical System Risk Assessment and Evaluation. The main contents of the evaluation include: 1) how to form the random sequence; 2) How to allocate the dose of drug administration; 3) How to implement the fixed blinding method by the leading researchers and the main research subjects of this research topic; 4) Analysis and evaluation of the impact indicators of the trial outcome; 5) How to ensure the accuracy and authenticity of data reports; 6) How to determine the research results of selective reporting; 7) Other potential biases. Two professional personnel conduct the selection, collection and quality evaluation of documents. In case of disagreement, they discuss with each other and reach a consensus.

2.5 Statistical methods

The research report of this paper selects the software revman5.3 application, which is based on the comprehensive quality analysis of the quality value evaluation and relevant data analysis information in the relevant literature. The ratio ratio (RR) and its 95% CI were used for the dichotomous variables, the standardized mean difference (SMD) and its 95% CI were used for the continuous variables, and the chi-square test was used to test the heterogeneity of the included study α=0.1, and observe the degree of heterogeneity according to I2 value. When P ≥ 0 1. When I2 ≤ 50%, it means that there is no significant clinical statistical heterogeneity among the participating groups in the study of this method, and the fixed effect random model analysis method is used to conduct a meta-random analysis; However, when the results P＜0.1 and I2＞ 50%, it indicates that the heterogeneity between the groups still exists, and further study and analysis of the data source of heterogeneity is needed. If there is no obvious statistical clinical heterogeneity, a meta-random effect analysis model needs to be established to conduct meta-random analysis of the results (Sun & Xu, 2014). If the published quantity of existing documents is sufficient, a funnel map form is used to help judge whether the documents are biased from the published direction of existing documents. If necessary, use the fixed effect calculation model and the random effect calculation model to calculate and estimate the result quality of different combination effects, and compare the consistency of the research results, so as to carry out sensitivity analysis for different research results.

3. Results

3.1 Literature search results

A total of 1152 documents were retrieved in this study, including 525 on HowNet, 376 on Wanfang, 216 on Vip, 19 on pubmed and 16 on Cochrane Library. In strict accordance with the inclusion and exclusion criteria, 13 documents were finally included in the study (J. Chen, 2016; M. Chen & Deng, 2016; Dai, Yan, & Lu, 2017; G, Zhong, & Kong, 2017; He & Lou, 2012; Hou, 2018; M. Liu, Shen, & Cheng, 2017; X. Liu et al., 2022; Shen, Yang, & Yang, 2013; Wu, Wu, & Liu, 2020; Xu, Zhao, & Huang, 2017; J. Zhang, Zhai, & Zha, 2017; Zhu, Xu, & Zhou, 2016).As shown in Figure 1.

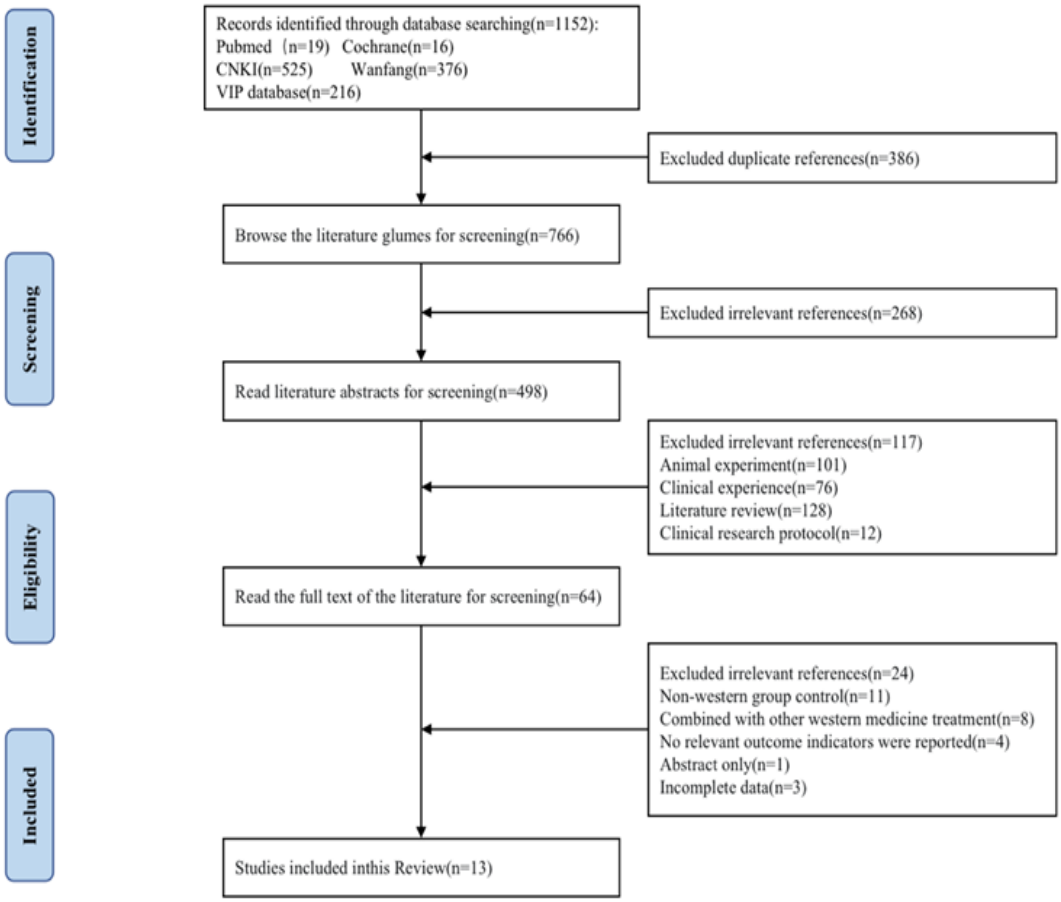


Figure 1: Literature screening process

3.2 Basic characteristics and quality evaluation of included documents

This study included 13 studies in total, 13 of which reported the effective rate of symptom improvement of athletic patients. 413 cases were included in the observation group, and the joint intervention of acupuncture and moxibustion and antiemetic drugs was taken, as shown in Table 1 and Table 2.

Among them, 4 used filiform needle acupuncture alone for acupuncture and moxibustion manipulation, 2 used electroacupuncture, 2 used warm acupuncture and moxibustion, 3 applied auricular points, 2 applied acupoints, and 9 articles had specific descriptions of acupoint selection; 411 athletic patients in the control group were treated with 5-HT3 antiemetic.

As shown in Figure 2, 13 included literatures all mentioned the use of random distribution, of which 8 included literatures mainly used the random number table method, 1 used the computer-generated random distribution method, 1 used the random envelope method, and the other 3 only mentioned random distribution; 13 articles did not explicitly mention the use of double-blind; The baselines of all literature groups have the same comparability. This study uses the bias risk assessment tool recommended by Cochrane collaboration network to evaluate the comprehensive quality of 13 relevant documents included in this study, of which 8 are of grade B and 5 are of grade A)

Table 1(a): Experimental design of inclusion study

INCLUSION STUDY	EXPERIMENTAL GROUP MALE/FEMALE（N）	CONTROL GROUP MALE/FEMALE（N）	EXPERIMENTAL GROUP INTERVENTION	CONTROL GROUP INTERVENTION	TREATMENT COURSE	OUTCOME INDICATORS
(M. CHEN & DENG, 2016)	17/12	20/10	Acupuncture+medicine	Granisetron hydrochloride	3 days	Nausea and vomiting symptoms、Acute and subacute toxicity of WHO anti-tumor drugs
(M. CHEN & DENG, 2016)	44/22	46/20	Acupuncture+medicine	Granisetron hydrochloride	6 days	Nausea and vomiting symptoms
(DAI ET AL., 2017)	23/7	20/10	acupoint application +medicine	Granisetron hydrochloride	5 days	Nausea and vomiting symptoms、NCI-CTC、RESIST、FLIE
(GE, ZHOU, & LIU, 2021)	32	32	Acupuncture+medicine	5-HT3	12 days	nausea and vomiting symptoms、NCI-CTCAE4.03
(X. LIU ET AL., 2022)	21/11	23/9	Auricular point sticking+medicine	Granisetron hydrochloride	8 days	nausea and vomiting symptom、food consumption、card score

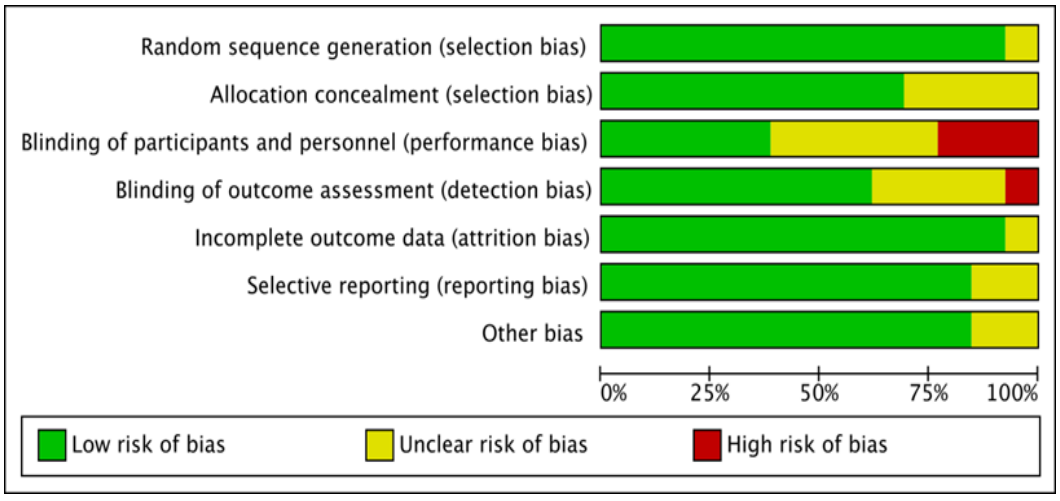
Table 1(b): Experimental design of inclusion study

INCLUSION STUDY	EXPERIMENTAL GROUP MALE/FEMALE （N）	CONTROL GROUP MALE/FEMALE （N）	EXPERIMENTAL GROUP INTERVENTION	CONTROL GROUP INTERVENTION	TREATMENT COURSE	OUTCOME INDICATORS
(HE & LOU, 2012)	14/10	13/12	Acupuncture+auricular points+ medicine	Granisetron hydrochloride	3 days	Nausea and vomiting symptom、Quality of life standards for cancer patients
(HOU, 2018)	28/16	27/17	Acupuncture+medicine	Granisetron hydrochloride	-	Nausea and vomiting symptom、FLIE
(M. LIU ET AL., 2017)	16/14	17/13	Acupuncture+medicine	Granisetron hydrochloride	5 days	Nausea and vomiting symptom 、Duration of vomiting and additional amount of antiemetic drugs
(SHEN ET AL., 2013)	16/14	17/13	Acupuncture+medicine	Granisetron hydrochloride	2 days	Nausea and vomiting symptoms
(WU ET AL., 2020)	16/14	18/12	Needle warming moxibustion+ medicine	Ondansetron hydrochloride	7 days	Nausea and vomiting symptoms
(XU ET AL., 2017)	20/17	21/16	Acupuncture+medicine	Granisetron hydrochloride	18 days	Nausea and vomiting symptoms
(J. ZHANG ET AL., 2017)	13/9	9/10	auricular points+ medicine	Ondansetron hydrochloride	-	Nausea and vomiting symptoms
(ZHU ET AL., 2016)	15/12	15/10	Electroacupuncture+ medicine	Palonosetron Hydrochloride	3 days	Nausea and vomiting symptoms

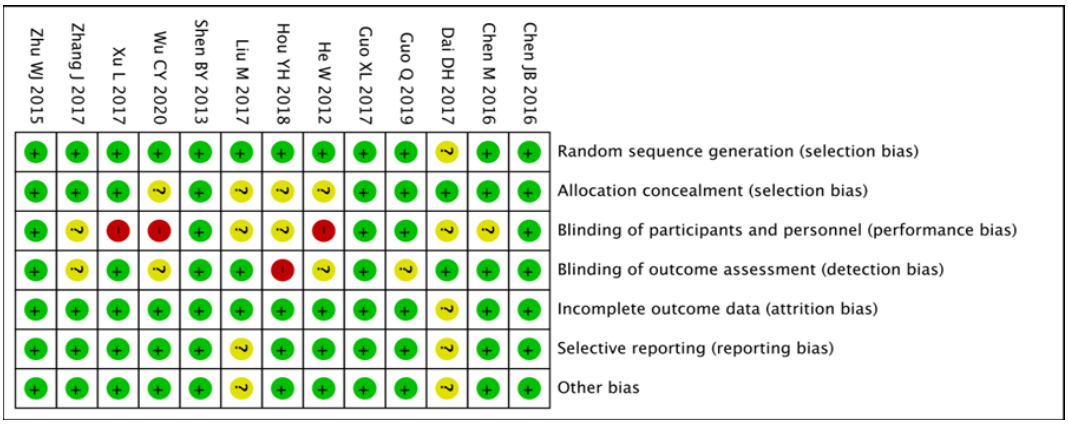
Table 2: Acupuncture mode and acupoint selection of the inclusion study

INCLUSION STUDY	ACUPUNCTURE MODE	SELECTED POINTS
(M. CHEN & DENG, 2016)	Milliacupuncture	ST36, ST25, RN12, PC6
(Y. CHEN, 2015)	Milliacupuncture	PC6, ST36, ST25
(DAI ET AL., 2017)	Milliacupuncture	LI11, PC6, ST36
GUO Q 2019	Milliacupuncture	RN12, ST36, PC6, SP4, ST25, RN6, RN4
GUO XL 2017	Auricular point sticking	HT7, stomach,large intestine,small intestine, sympathy,Ashi-acupoint
(HE & LOU, 2012)	Auricular points	RN12, PC6, LI10, ST36, SP4, Auricular points
(HOU, 2018)	Milliacupuncture	LI11, PC6, ST36
(M. LIU ET AL., 2017)	Milliacupuncture	RN6, RN4, ST36、PC6
(SHEN ET AL., 2013)	Milliacupuncture	ST36, PC6
(WU ET AL., 2020)	Needle warming moxibustion	ST36, PC6, LI4
(XU ET AL., 2017)	Milliacupuncture	ST36, ST25, PC6, RN12, SP3, SP9, LR3
(XJ ZHANG & ZHANG, 2006)	auricular points	HT7, sympathy,spleen,stomach,subcortex
(J. ZHANG ET AL., 2017)	Electroacupuncture	Vagus,Superior point of vagus

3.3 Meta analysis of effective rate of symptom improvement (nausea and vomiting)



A



B

Figure 2: Risk of bias graph A: risk of bias item among included studies; B: risk of bias item in each included study.

Figure 2 shows that a total of 13 articles are included in the literature, and the outcome index includes the effective rate of inhibiting gastrointestinal symptoms. For some medical documents (Dai et al., 2017; G et al., 2017; X. Liu et al., 2022; J. Zhang et al., 2017) that do not classify athletic patients with effective treatment, to determine whether there is nausea, vomiting and diarrhea at the completion of treatment; Grade I: nausea, but normal appetite, vomiting once within 24 hours, grade 0, grade 1 and grade 1 are classified as effective. Grade II: nausea, decreased appetite, but able to eat, vomiting 2 to 5 times within 24 hours, Grade III: nausea, unable to eat significantly, vomiting 6 to 10 times within 24 hours, Grade IV: nausea, unable to eat; Vomiting>10 times within 24 hours requires gastrointestinal support treatment, and this grade 2, 3 and 4 is classified as invalid. In the test of heterogeneity, the outcome indicators were not statistically heterogeneous (P=0.35, I2=10%). The fixed effect model analysis showed that acupuncture combined with 5-HT3 receptor antagonist was better than 5-HT3 receptor antagonist alone in treating CINV after chemotherapy [RR=1.27, 95% CI (1.18, 1.37), P<0.00001] (Figure 3).

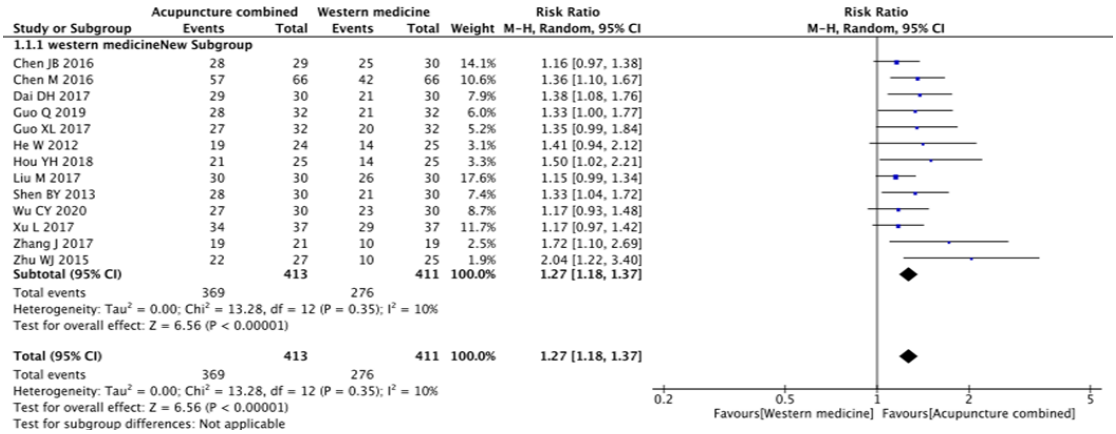


Figure 3: Meta-analysis of the effective rate of acupuncture combined with western medicine compared with antiemetic drugs

Figure 4 shows that through Revman 5.3, the statistical software draw a funnel map of the total effective rate of CINV after chemotherapy treated by acupuncture combined with 5-HT3 receptor antagonist, and the results showed that the funnel map was not symmetrical and might have bias.

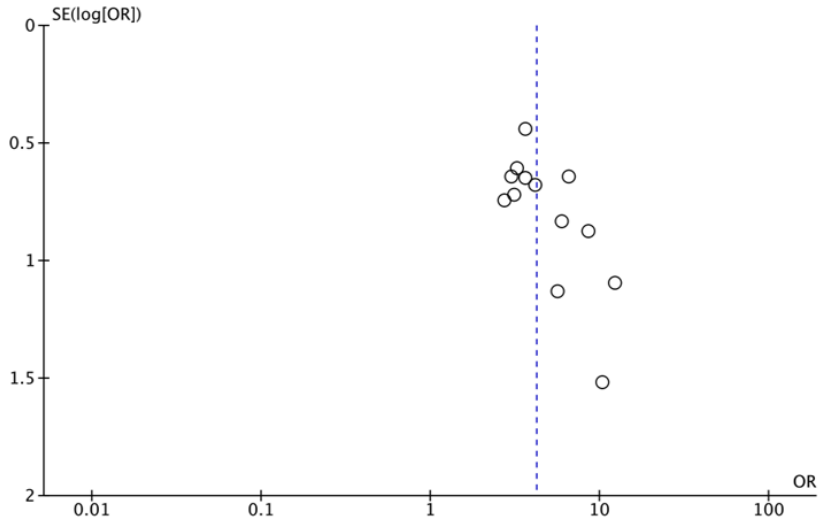


Figure 4: Funnel diagram of total efficiency

4. Discussion

Chemotherapy-related nausea and vomiting belongs to the field of "vomiting" in traditional medicine. Vomiting symptoms are mainly caused by the loss and decline of stomach function, and the inversion of stomach qi, which makes the contents of stomach vomit through the esophagus and mouth. From the perspective of modern medicine, CINV vomiting response is coordinated by the brain vomiting center located in the medulla oblongata. This vomiting center integrates various peripheral and central input pathways, causing vomiting reflex. The peripheral pathway originates from the gastrointestinal tract, which stimulates the expansion of the stomach and duodenum through the abdominal vagus nerve. The receptors in this group can trigger vomiting reaction when stimulated, and 5-HT3 is one of the main mediators (Gupta, Walton, & Kataria, 2021). Therefore, 5-hydroxytryptamine receptor antagonist has become one of the commonly used antiemetics in clinical practice at present. It has a good effect on nausea and vomiting (CINV) caused by acute chemotherapy, but has a slight effect on delayed vomiting (Ge et al., 2021; X Zhang & Fan, 2014). Moreover, the main adverse reactions such as liver function damage, rash, constipation cannot be ignored (Y. Chen, 2015). In this meta-analysis, it was found that the use of acupuncture and moxibustion combined with western medicine can greatly improve its effectiveness and reduce the occurrence of adverse reactions. As for the selection of acupoints, as shown in Table 3, according to the statistics of 13 documents included in the study, Zusanli and Neiguan are the most frequently used. Zusanli is the combination point of the

stomach meridian and the lower combination point of the large intestine meridian, which can nourish the spleen and stomach, regulate qi and blood, and enhance immunity. Through research, it has a good preventive and therapeutic effect on gastrointestinal mucosal damage and central gastrointestinal reaction caused by chemotherapy drugs. Neiguan point is the collateral point of the pericardial meridian, which is connected with the triple energizer meridian, which can communicate the external and internal meridians and dredge the triple energizer qi. Experimental research has proved that Neiguan has an obvious regulating effect on the disorder of qi and nervous system of esophagus, cardia and pylorus. Acupuncture of Neiguan can inhibit gastric hyperkinesia, reduce intragastric pressure, and antagonize abnormal stimulation of gastric hyperkinesia (Ge et al., 2021).

Table 3: Frequency of selected acupoints

POINT	FREQUENCY	POINT	FREQUENCY	POINT
ZUSANLI	10	Guanyuan	2	
NEIGUAN	10	Gongsun	2	
ZHONGWAN	4	Shousanli	1	
TIANSHU	4	Hegu	1	
QUCHI	2	Taibai	1	
QIHAI	2	Yinlingquan	1	
		Taichong	1	

However, the acupuncture points are still taken according to the conventional principles of anti-vomiting acupuncture points, without considering the evidence of the type of treatment. In TCM theory, chemotherapy drugs are "poisonous", nausea and spleen and stomach belong to the category of spleen and stomach malfunction, "poisonous" damage to the spleen and stomach, disturbing the qi of middle-jiao energy causing the Qi of stomach to rebel, resulting in nausea and vomiting, which are due to the cold and heat toxicity of chemotherapy drugs. The GI reactions that occur after the clinical application of chemotherapeutic drugs mostly belong to the cold and hot type, and the points with the properties of cold and heat can be used to balance Yin and Yang in response to the deficiency of cold and heat in the spleen and stomach. Therefore, not only can we in the selection of acupuncture points can be selected dialectically, but also in the specific method of acupuncture in the treatment. Current research has found that milli-acupuncture can effectively help regulate the neuro-endocrine system and improve the function of the body's own immune system; acupuncture acts on the human digestive system, lowering the human serum concentration of GAS and raising the serum MLT value through acupuncture, balancing the digestive movement of the human gastrointestinal tract; in addition, acupuncture and moxibustion of the foot San Li point may improve the peripheral P substance content; electroacupuncture stimulates the NeiGuan and in addition, acupuncture and moxibustion at the

Sesanli point may improve the peripheral P-substance level; electroacupuncture stimulation at the Neiguan and Zhanguan points, which are commonly used to stop vomiting, may be related to the reduction of 5-HT and DA receptors (Gupta et al., 2021). It stimulates the ability of the human body to self-balance and regulate the excitability of the vagus nerve, inhibits the formation of pathological foci of excitation in the cerebral cortex, and reduces the stimulation of the vomiting center in the medulla oblongata by the afferent vomiting signals (Zhu et al., 2016). The limitations of this study are mainly as follows: First, there are few included documents and the quality rating is uneven. Also, the sample size is not estimated and the use of random distribution is not standardized. In addition, there is a lack of distribution concealment、blind method、follow-up and review, and the risk of bias is high; Second, the treatment course and outcome indicators of different documents are different， the maximum treatment course of the included documents is 18 days, and the minimum is 2 days; Third, the outcome indicators are not enough，in which only few documents have been collected, such as the comparison of vomiting symptoms before and after treatment, the quality of life score, and the subjective evaluation of athletic patients, so that the treatment effect cannot be evaluated more comprehensively. This study conducted an objective and systematic evaluation of the efficacy of acupuncture and moxibustion combined with antiemetics in the treatment of chemotherapy related vomiting through Meta analysis. The results showed that the total effective rate of acupuncture and moxibustion assisted antiemetics was significantly better than that of antiemetics alone, which could effectively improve the nausea and vomiting symptoms ofathletic patients, strengthen the spleen and move the stomach, partially reduce the occurrence of headache, dizziness, diarrhea, rash and other adverse reactions caused by antiemetics, thus helping athletic patients overcome their fear of chemotherapy side effects and improve their treatment compliance. It was a feasible method for clinical treatment of upper gastrointestinal reactions after chemotherapy. However, due to the influence of the quantity and quality of the included documents, there are still some limitations. In the future, we should add a unified baseline (such as the TCM syndrome type, stage, severity of vomiting symptoms, etc. of specific cancer), and correctly use randomized, blind, multiple clinical trials of central and heavyweight samples to ensure the reliability of the results; You can also select different acupoints for different cold and heat athletic patients according to the different cold and heat attributes of the chemotherapy program.

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