A Journal of the Bangladesh Pharmacological Society (BDPS)
Journal homepage: www.banglajol.info
Abstracted/indexed in Academic Search Complete, Asia Journals Online, Bangladesh Journals Online, Biological Abstracts, BIOSIS Previews, CAB Abstracts, Current Abstracts, EMBASE/Excerpta Medica, Google Scholar, HINARI (WHO), International Pharmaceutical Abstracts, Open J-gate, Science Citation Index Expanded, SCOPUS and Social Sciences Citation Index;
Bangladesh J Pharmacol 2016; 11: 793-801
ISSN: 1991-0088

Meta-analysis

Systematic review and meta-analysis of shenqi fuzheng and chemotherapy combination in the treatment of breast cancer

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Article Info

Received: 31 March 2016
Accepted: 1 June 2016
Available Online: 1 October 2016

DOI: 10.3329/bjp.v11i4.27200

Cite this article:
Li Y, Han N, Chen Z, Li X. Systematic review and meta-analysis of shenqi fuzheng and chemotherapy combination in the treatment of breast cancer Bangladesh J Pharmacol. 2016; 11: 793-801.

Abstract

This review evaluates the effectiveness and safety of injection of shenqi fuzheng with chemotherapy in the treatment of breast cancer in China. The study included 20 randomized clinical trials (RCTs) involving 1,609 patients. It was shown that shenqi fuzheng could improved the treatment efficiency, Kamofsky Performance Status (KPS), weight and autoimmune; reduced fatigue, gastrointestinal reaction and the toxicity of bone marrow; protected liver, kidney and heart from damage by chemotherapy. However, the quality of all the studies was relatively low and there was great heterogeneity between various studies. Further well-designed research is needed to estimate the beneficial effects of shenqi fuzheng.

Introduction

The morbidity of breast cancer had been more than cervical cancer in many Western countries and had been highest in gynecological tumors (Pu et al., 2015). Cancer statistics show that breast cancer is the most frequently diagnosed cancers (Horton et al., 2015). A total of 565,469 cancer deaths were reported in USA in 2008, for which practical data are effective at the most recent years (Lee et al., 2014). Cancer is the second leading cause of death (23% of all death) following heart disease. From 2007 to 2008, the cancer death rate reduced 1.5%, from 178.4/100,000 to 175.8 (Raia-Barjat et al., 2014). At present, the incidence of breast cancer rose by 3-4% each year which was higher than the global average growth rate in China (Valadares et al., 2013).

Chemotherapy has been an important method of adjuvant treatment of breast cancer. It has a lot of problems in the use to treat breast cancer (Schmidt et al., 2015). Toxic and adverse effects of chemotherapy have a strong impact on adjuvant treatment of breast cancer. Some patients cannot accomplish treatment in accordance with the original plans of adjuvant treatment of breast cancer (von Minckwitz et al., 2014). When chemotherapeutics acted on the tissues of breast cancer patient, its specific inhibitory effects on cancer cell were weaker. At the same time, chemotherapeutics could kill a large number of normal cells of breast cancer, so with the result that sufferers usually complain nausea, vomiting, inappetence, leukopenia, multiple organ function lesion, and exhaustion syndrome (McCarthy et al., 2014).

Reduce the adverse effects of chemotherapy is important in the treatment of breast cancer. Shenqi fuzheng mainly contains pilose asiabell root and Mongolian milkvetch root. It has cardioprotection, antifatigue, immunity enhancement, replenishing blood, increase the function of spleen and kidney, improve the secretion of hematopoietic factor and lymphocyte, extend survival of cell and so on (Yao et al., 2014). Pharmacological studies have shown that pilose asiabell root and Mongolian milkvetch root can activate T-cell and enhance macrophage phagocytosis, improve the body's immune function, adjust the metabolism of body cell, have fight oxidation and inhibit the bone marrow

toxicity of chemotherapy drugs and so on (Ai et al., 2014). Astragalus inhibits the proliferation of breast cancer cell lines (MDA-MB-468; MDA-MB-231). At the same time, the effects of astragalus on MDA-MB-468 cell and mMSCs are related to the concentration of astragalus (Deng and Chen, 2009) and its mechanism of inhibiting the proliferation of MDA-MB-468 cell might be due to down-regulation of the expressions of EGFR and p53 protein (Ye and Chen, 2008).

At present, the quality of many RCT with shenqi fuzheng and chemotherapy combination in the treatment of breast cancer was uneven. At the same time, there was system assessment about shenqi fuzheng combined with chemotherapy in the treatment of breast cancer. Therefore, it is necessary to make a system evaluation of RCT of shenqi fuzheng combined with chemotherapy in the treatment of breast cancer, and provide a reference for clinic treatment and future studies.

Materials and Methods

Literature search

The following databases were used for literature search: CBM, CNKI, VIP, Wangfang Data, Springer Link, EBSCO, PubMed, MEDLINE and Embase. The selected RCT of shenqi fuzheng combined with chemotherapy in the treatment of breast cancer were collected. The reference lists of papers were authenticated and scanned for further trials. The under search labels were used conjunctively or individually: 'Postoperative breast cancer', 'Breast Cancer', 'Chemotherapy', 'Shenqi fuzheng injection', 'Randomized controlled trial', and 'Clinical trial'. All of these literatures were updated up to May, 2015.

Inclusion criteria: All the articles of RCT about shenqi fuzheng in the treatment of breast cancer with chemotherapy were assessed including the following parameters: the object of study: the female breast cancer patients; the intervening measure of experimental group: shenqi fuzheng plus standard chemotherapy; the intervening measure of control group: the standard chemotherapy; the assessment criteria: the treatment efficiency, physical condition autoimmunity, protected main organs, reduced the toxicity of bone marrow, etc; the course of treatment ≥4 weeks; full-text document.

Exclusion criteria: The literatures that had been not included were as follows: the duplicate publication literature; the literature could not provide the basic information of subjects or the relevant information of intervening measure.

Quality assessment

Two authors independently worked for literature searching, studied choice, and extraction of data. When there was any disagreement, then it was solved by discussion. Xing Li guided the overall process of this study. The abstracted data included were as follows: title, authors, time of publication, information on methodology, sex, control interventions, treatment, outcomes and adverse drug reaction. The assessment tool was used to assess all studies to address the following seven criteria (Cochrane 5.1.0 Handbook of Systematic Reviews of Interventions): randomization, allocation concealment, blinding, loss of imitation and exit cases, intention-to-treat analysis, baseline and Cochrane score. These studies which met the standards were a) low risk of bias, b) unclear risk of bias, c) high risk of bias, and if insufficient information acquired to make judgment.

Data extraction

We read the title, summary as well as full text of all included studies to extract the data. Two researchers independently conducted the quality assessment and discussed the quality of each paper with each other and finally made a decision.

Data analysis

RevMan 5.2 software was used for meta-analysis. Clinical heterogeneity and methodological heterogeneity of the included studies were analyzed. When statistical results with p value <0.05, the difference was considered as statistically significant. Meta-analysis was utilized if the studies had receivable homogeneity of study design, controls, interventions, participants, and out-come measures. The heterogeneity test results, $p<0.1$, $I_2 \geq 50\%$, we adopted random effects model (REM); $p>0.1$, $I_2 < 50\%$, we adopted fixed effect model (FEM) (Shui et al., 2015). Data was summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary outcomes or mean difference (MD) with a 95% CI for continuous outcomes. Publication bias was explored by way of a funnel-plot analysis (Pu et al., 2014). Missing or lost to cases count data should be counted as treatment failure cases. So, we have demonstrated the sensitivity analysis, if the research indicators contained more than 10 RCT and used funnel plot to check the presence of publication bias; if research indicators contained less than 10 RCT and did not check.

Results

Studies

Seven databases were searched for screening of 1,497 documents. Duplicate documents (1,019) were eliminated by way of hand searches and electronic. The eliminated 959 documents were 'time too long' or the 'no-research object'. We eliminated non-randomized controlled trial/interventions and the results have not met the inclusion criteria by reading abstract (60 documents). We eliminated 27 documents with data in

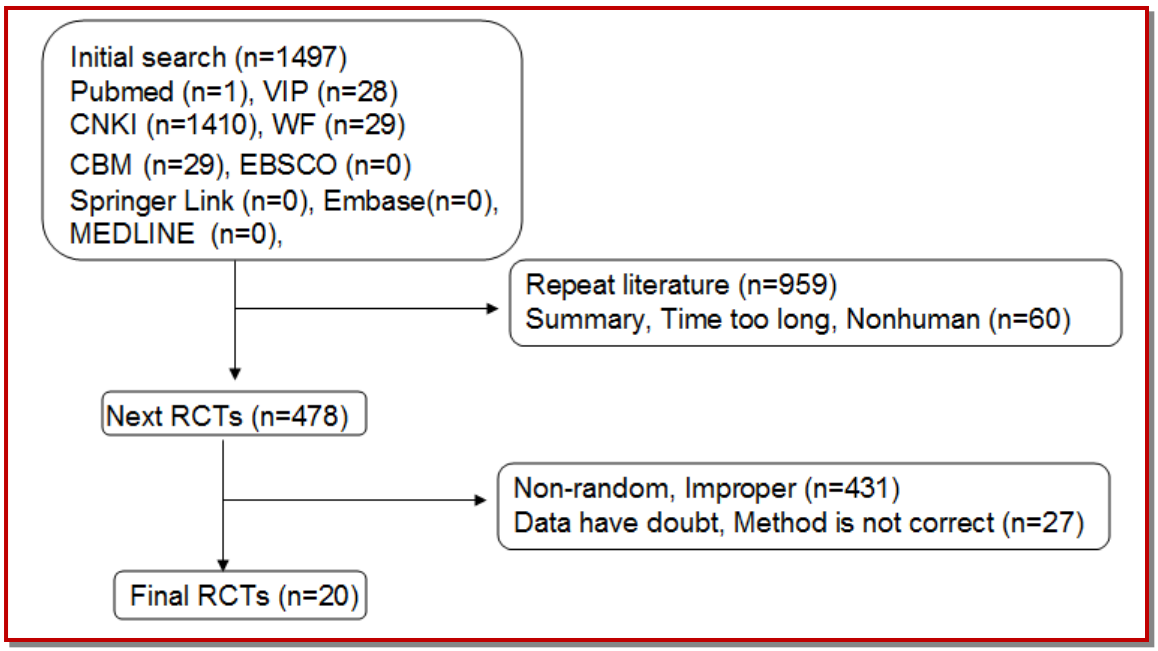

Figure 1: Flowchart of identification of studies included in the review

question/random method is not correct by reading full text. Finally full-text papers of 20 studies were searched from all the citations. A flow chart described the search method and study chose (Figure 1).

General characteristics

There were 20 trials literature containing 1,609 cases (shenqi fuzheng group: 831 cases and chemotherapy group: 778 cases). In this study, the largest number of cases in RCT was 185 and the least number was 40. The features of studies were mentioned in Table I.

Quality of methodology of RCT

We made a system evaluation of all the included studies in accordance with the 'Cochrane 5.1.0 Handbook of Systematic Reviews'. All the included studies were categorized to low risk of bias. All studies had no sample estimate and belonged to low quality (Table II).

Meta-analysis

Effective treatment: Five trials (526 patients) reported the effectiveness of shenqi fuzheng treatment (180/265) and shenqi fuzheng combined with chemotherapy (138/261). The heterogeneity test results p=0.04, I_2=60%, we had chosen fixed effect model (FEM). Z=2.35, RR =1.35, 95%CI [1.05~1.73], p=0.02. The results showed, the treatment efficiency of shenqi fuzheng combined with chemotherapy in treatment of breast cancer was significantly higher than the control group, compared the difference was significant (Figure 2).

Nutritional status

Kamofsky performance status: The eight trials reported that shenqi fuzheng improved patient's Kamofsky performance status in treatment of breast cancer with chemotherapy, which included 610 patients, shenqi fuzheng group and chemotherapy group were 253/321, 143/289, respectively. The heterogeneity test results p=0.42, I_2=1%, we had chosen FEM. Z=7.00, RR=1.58, 95% CI [1.39~1.79], p<0.00001. The results show, shenqi fuzheng was significantly higher than the control group in treatment of breast cancer patient's Kamofsky Performance Status with chemotherapy, compared the difference was significant (Figure 3).

Weight gain: The two trials reported that shenqi fuzheng gained patient's weight in the treatment of breast cancer with chemotherapy, which included 218 patients, shenqi fuzheng group and chemotherapy group were 93/113, 32/105, respectively. The heterogeneity test results p=0.10, I_2=63%, we had chosen REM. Z=3.79, RR=2.70, 95% CI [1.62~4.52], p<0.00001. The results show, that shenqi fuzheng was significantly higher than the control group in treatment of breast cancer patient's weight with chemotherapy, compared the difference were significant (Figure 4).

Reduction of fatigue: The two trials reported that shenqi fuzheng reduced patient's fatigue in treatment of breast cancer with chemotherapy, which included 132 patients, shenqi fuzheng group and chemotherapy group were 23/66, 52/66, respectively. The heterogeneity test results p=0.12, I_2=58%, we had chosen REM. Z=2.71, RR=0.44, 95% CI [0.24~0.79], p=0.007. The results show, shenqi fuzheng was significantly higher than the control group in treatment of breast cancer patient's fatigue with chemotherapy, compared the difference was significant (Figure 5).

Protect the bone marrow suppression situation and the

Table I

Baseline characteristics of the eligible trials

Reference	Randomi-zation	Allocation concealment	Form of double-blind	Loss of imitation and exit cases	ITT analysis	Baseline	Cochrane score
Xiao et al., 2005	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Chen et al., 2007	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Xu et al., 2010	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Chen et al., 2010	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Yuan et al., 2008	Random number	Unclear	Unclear	Unclear	Unclear	Yes	C
Lie et al., 2005	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Kawuli et al., 2011	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Zhu et al., 2007	Random number	Unclear	Unclear	Unclear	Unclear	Yes	C
Xu et al., 2003	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Lu et al., 2010	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Zhang et al., 2004	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Wang et al., 2006	Random number	Unclear	Unclear	Unclear	Unclear	Yes	C
Zou et al., 2006	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Li et al., 2004	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Sun et al., 2011	Mention	Unclear	Unclear	Clear	Unclear	Yes	C
Li et al., 2002	Random number	Unclear	Unclear	Unclear	Unclear	Yes	C
Cui et al., 2011	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Ze et al., 2011	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C
Huang et al., 2008	Random number	Unclear	Unclear	Unclear	Unclear	Yes	C
Dai et al., 2007	Mention	Unclear	Unclear	Unclear	Unclear	Yes	C

important organs of the patient: Shenqi fuzheng could protect effectively breast cancer patient's bone marrow adverse reactions and important organs during chemotherapy, was significantly higher than the control group, compared the difference was significant. These adverse reactions included nausea and vomiting, leukopenia, thrombocytopenia, decreased hemoglobin, cardiac injury, liver injury and kidney injury (Table III).

Activity of T cell subsets and NK cells: In summary, shenqi fuzheng could increase effectively the activity of breast cancer patient's T cell and NK cells during chemotherapy, was significantly higher than the control group, compared the difference was significant (Table IV).

Heterogeneity analysis: The study had 16 indicators in which 7 indicators (I^2 <25%) were considered good homogeneity and developed a meta-analysis. 1 indicator (25%<I_2<50%) was considered mild heterogeneity and chosen FEM. 5 indicators (50%<I_2<75%) were considered moderate heterogeneity and chosen REM. 3 indicators (I_2>75%) was considered high heterogeneity and chosen REM. We analyzed the causes of heterogeneity and found that methods, technological means and time of measurement were very variable in different years and different areas. These differences might bring about heterogeneity of these indicators in the study. At the same time, the evaluation criterions of better homogeneity indicators was relatively objective, so their study result had good homogeneity.

Table II

Methodological quality scores

Reference	Sample size (Rx = C)	Age (Year, Rx = C)	Experimental intervention	Control intervention	Duration of treatments
Xiao et al., 2005	55/53	56.7	SI + CEF	CEF	8 days SI; 8 days CEF
Chen et al., 2007	34/34	51	SI + CEF	CEF	6 × 24 days SI; 6 × 21 days CEF
Xu et al., 2010	28/24	47/49	SI + TA	TA	7 days SI; 21 days TA
Chen et al., 2010	90/95	42/45	SI + TD	TD	2~3 days SI; 21 days TD
Yuan et al., 2008	38/35	38/35	SI + CAF	CAF	3 × 20 days SI; 3 × 20 days CAF
Lie et al., 2005	30/30	56/57	SI + 5-FU + Navelbine	5-FU + Navelbine	7 days SI; m 21 day 5-FU + Navelbine
Kawuli et al., 2011	40/40	46	SI + TA	TA	3 × 7 days SI; 3 × 21 days TA
Zhu et al., 2007	32/24	52.5/51	SI + CEF	CEF	4 × 10 days SI; 4 × 21 days CEF
Xu et al., 2003	53/59	-	SI + CAF	CAF	8 days SI; 21 days CAF
Lu et al., 2010	58/52	58.5	SI + CAF	CAF	2~3 × 2 weeks SI; 2~3 × 3 weeks CAF
Zhang et al., 2004	26/30	-	SI + CAF	CAF	8 days SI; 21 days CAF
Wang et al., 2006	40/32	45.2 ± 9.8/ 46.7 + 10.5	SI + CMF	CMF	6 × 8 days SI; 6 × 21 days CMF
Zou et al., 2006	32/32	52.5	SI + CTE	CTE	2 × 14 days SI; 2 × 14 days CTE
Li et al., 2004	40/35	56.4/54.2	SI + NE	NE	10 days SI; 3 × 28 days NE
Sun et al., 2011	60/45	55	SI + CMF	CMF	4 × 28 days SI; 4 × 28 days CMF
Li et al., 2002	35/27	47.2 ± 10.8/ 46.7 ± 10.5	SI + CAF	SI + CAF	3 × 21 days SI; 3 × 21 days CAF
Cui et al., 2011	22/20	52	SI + CAF, AC	FAC, AC	4 × 5 ~ 8 days SI; 4 × 21 days FAC, AC
Ze et al., 2011	23/20	43	SI + Chemo-therapy	Chemother-apy	2 ~ 4 × 10 days SI; 2 ~ 4 × 21 days Chemotherapy
Huang et al., 2008	30/30	47/46	SI + CTF	CTF	2 × 28 days SI; 2 × 28 days CTF
Dai et al., 2007	65/61	45.5 ± 26.8/ 46.1 ± 27.5	SI + CEF	SI + CEF	2 × 28 days SI; 2 × 28 days CEF

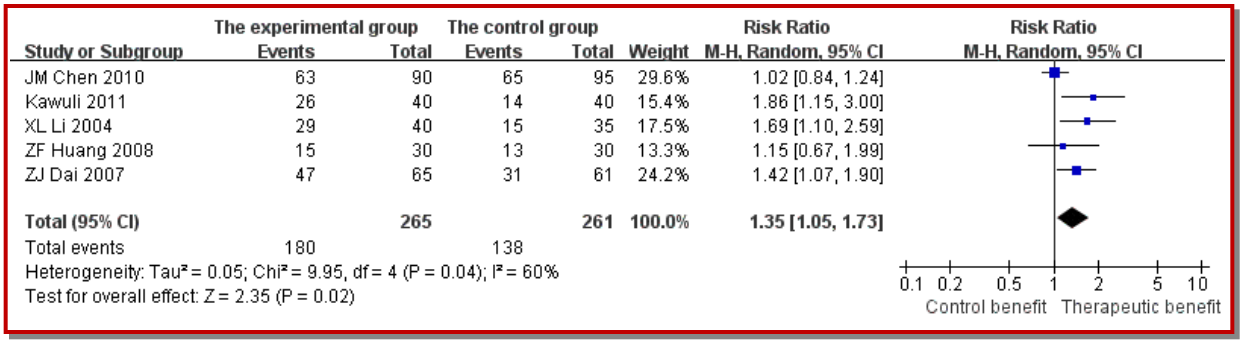

Figure 2: Treatment efficiency of SI in treatment of breast cancer with chemotherapy

Discussion

Chemotherapeutics have cytotoxicity, can inhibit tumor cell growth and kill normal cells, and restrain hematopoietic system (Sanchez et al., 2014). At the same time, chemotherapeutics can treat breast cancer with traditional Chinese medical science, which can reduce significantly side effects and ensure the completion of chemotherapy treatment (Li et al., 2015).

Shenqi fuzheng can promote proliferation role of T cell subsets and improve the T cell immunity. Shenqi fuzheng often used to cure various kinds of immunocompromised patients in clinical, such as

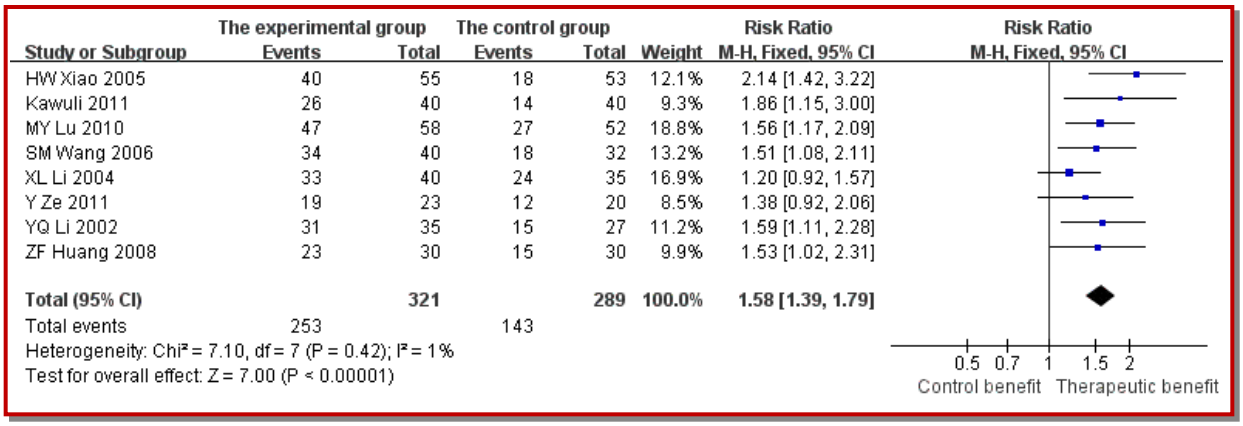

Figure 3: KPS of SI in treatment of breast cancer with chemotherapy

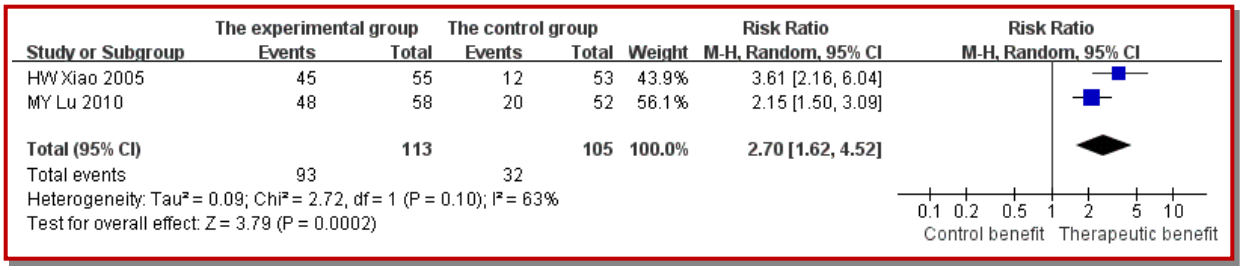

Figure 4: The weight of SI in treatment of breast cancer with chemotherapy

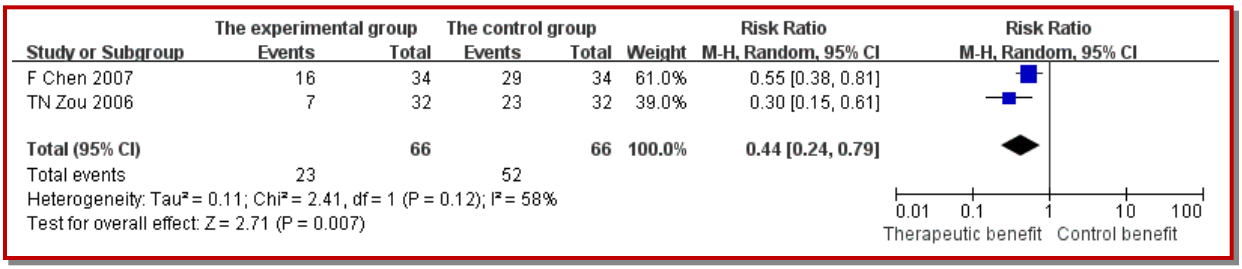

Figure 5: The fatigue of SI in treatment of breast cancer with chemotherapy

recurrent respiratory tract infection, postoperation of chemotherapy and radiotherapy, and chronic and serious illness. Shenqi fuzheng can improve the body's immune function, shorten the course and invigorate health effectively of breast cancer (Bo et al., 2007). Many researches show that Mongolian milkvetch root can produce erythrocyte and granulocyte of bone marrow cells, treat significantly leucopenia (Xie et al., 2011). Pilose asiabell root can increase the red blood cells, white blood cells and hemoglobin. Shenqi fuzheng has supporting the healthy energy, "Yiqi Jianpi", antifatigue, adjustion of humoral and cell-mediated immunity, protection of bone marrow function, and reduces adverse effects of chemotherapeutics to heart by means of angiectasis and improve circulation (Lin et al., 2013). Modern pharmacology explain that Mongolian milkvetch root can improve directly or indirectly the ability of adrenal cortex and has a strengthening and restoring and promoting the health effect. Mongolian milkvetch root can improve the anti-neoplastic activity by means of increased proliferation of T cell and increase the capability of lymphocyte transformation (Lu and Chen, 2003).

Comprehensive literature evaluation, clinical effects of shenqi fuzheng combined with chemotherapy in treatment of breast cancer included: shenqi fuzheng could enhance treatment efficiency (p=0.02); shenqi fuzheng could improve the nutritional situation of patient, improve patient's Kamofsky performance status (p<0.00001) and weight (p=0.0002), and reduce patient's fatigue (p=0.007); shenqi fuzheng could protect the bone marrow suppression situation of patient, increase the number of leucocyte (p<0.00001), hematoblast (p=0.02) and hemoglobin (p<0.00001), and reduce nausea and vomiting (p<0.0001); shenqi fuzheng could protect the main organs, protect the liver (p=0.007), kidney (p=0.008) and heart (p=0.0007); shenqi fuzheng could increase the activity of T cell subsets and NK cells (p<0.00001).

The evidence-based medicine emphasizes that scientific evidence should be organically combined with clinician's decision-making and patients' own intents. The conclusion of this study pays more attention to the

Table III

SI protect bone marrow adverse reactions and important organs

The indexes	Literature	SI group	Control group	Heterogeneity	Model	RR/MD [95% CI]	p value
Nausea/ vomiting	5 trials	108/304	184/276	p = 0.03, I2 = 63%	REM	RR = 0.53, [0.38, 0.72]	p<0.0001
Leukopenia	6 trials	258	252	p = 0.19, I2 = 33%	FEM	MD = 1.39, [1.02, 1.76]	p<0.00001
Thrombocy-topenia	6 trials	258	252	p = 0.60, I2 = 0%	FEM	MD = 13.25, [2.45, 24.04]	p = 0.02
Hemoglobin	5 trials	203	199	p = 0.73, I2 = 0%	FEM	MD = 10.82, [7.44, 14.21]	p<0.00001
Cardiac trau-ma	5 trials	36/180	60/159	p = 0.37, I2 = 7%	FEM	RR = 0.58, [0.42, 0.79]	p = 0.0007
Liver injury	2 trials	12/100	22/80	p = 0.29, I2 = 9%	FEM	RR = 0.42, [0.23, 0.79]	p = 0.007
Kidney injury	2 trials	7/100	16/80	p = 0.46, I2 = 0%	FEM	RR = 0.33, [0.15, 0.75]	p =0.008

Table IV

SI increase the activity of breast cancer patient's T cell and NK cells

Time	Number of trials	SI group/Control group	Heterogeneity	Model	MD [95% CI]	p value
CD3	5	263/256	p = 0.03, I2 = 61%	REM	9.60 [8.66, 10.53]	p<0.00001
CD4	6	205/185	p<0.00001, I2 = 94%	REM	11.43 [10.51, 12.35]	p<0.0001
CD8	4	182/168	p<0.00001, I2 = 96%	REM	4.29 [3.50, 5.07]	p<0.00001
CD4/CD8	7	310/298	p = 0.26, I2 = 23%	FEM	11.43 [10.51, 12.35]	p<0.00001
NK cells	5	228/214	p<0.00001, I2 = 84%	REM	6.01 [3.26, 8.76]	p<0.0001

statistical significance and differences. Before clinical application, experts and scholars' experience of diagnosis and treatment should be combined, and patients' own intents should also be fully considered to comprehensively evaluate the clinical significance of this conclusion.

In the 20 RCT included in this evaluation, 4 studies (5/20) described the specific random method, the other experiments mention "Random". None reported allocation concealment, double-blind method, ITT analysis, and loss of imitation and exit cases. Baseline of all studies was no difference. However, the intention-to-treat principle was not adopted for data analysis. All the included RCT have the word "random" in their reports, but they neither describe the randomized order nor the allocation concealment. And only part of them mentions about the used random methods. While in the RCT published in domestic core journals, coverage rate of the randomized order is 48.9% (Schulz, 2001). Improper use of random method or false random may cause selective bias and have enormous influences upon the test results. Randomized allocation concealment in foreign RCT is as high as 48%. Allocation concealment also plays an important role in preventing bias and randomization. Without allocation concealment, the intervention effect can be exaggerated by an average of 30-41% (Moher et al., 2010). This is the deficiency of the study. At the same time, all documents are compared with the patients' baseline data, such as the pathological grading and staging and treatment plan, the results have shown that the baselines between experimental group and the control group are comparable (p>0.05).

These 20 trials literature included the average number of 41.6 cases in shenqi fuzheng plus chemotherapy group and 38.9 cases in chemotherapy group. 5 studies (5/20%) were study population ≥100 cases. There were no the estimated sample size in all research. Sample size of all trials was too small, which increased incidence of type II error and reduced the accuracy of the test results. This is the inadequate research. At same time, the important factor was the low-quality RCT.

In the 20 RCT included in this systematic review, only 14 RCT took the pathological diagnosis as the standard

for the judgment of breast cancer, while none of the rest literature had mentioned the diagnostic criteria. There were 11 RCT that have described the stages of breast cancer, in which only 4 RCT adopt UICC or TNM standard. And there were only 7 RCT that had described the types of breast cancer and SI of 14 RCT came from 'Limin pharmaceutical factory'. The non-unified diagnostic criteria, undefined stages and types, as well as the inconsistent source of administered medicine had affected the meta-analysis results.

Any kind of treatment measures or therapeutics may cause untoward effects in various extents. The monitoring on untoward effects of drug intervention has important significance for guiding clinical medication and evaluating drug efficacy. However, the literature involved in this study has only reported the untoward effects, while it is unclear whether there are untoward effects in the research process of other experiments, indicating that the researchers do not pay sufficient attention to the observation and report of untoward effects. This will be adverse to the application and promotion of SI treatment for breast cancer.

Conclusion

Currently the methodology and reports of clinical research on the combination of shenqi fuzheng and chemotherapy to treat breast cancer are with low quality, and cannot provide scientific and reliable basis for clinical application. So, it suggests following the standard of the multi-center and large-sample randomly controlled double-blind trials to design the experiments rather than the low-level duplicates.

Conflict of Interest

The authors have no collisions of interest to disclose.

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