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Therapeutic effect and safety of xiaoqinglong decoction and sanziyangqin decoction in children with cough variant asthma: a Meta-analysis

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Abstract: Objective: To evaluate the therapeutic effect and safety of xiaoqinglong decoction and sanziyangqin decoction combined with western medicine in children with cough variant asthma. Methods: Using the computer to retrieve literatures in The databases CNKI, WangFangData, VIP and PubMed, which published in October 2022 about the relevant clinical research, according to the row of standards to determine the literature, extract the data, the use of the Cochrane bias risk assessment tools for quality assessment included in the article, by using RevMan 5.4.1 software for meta-analysis articles. Results: A total of 14 RCTs involving 1268 patients were included. The results of the Meta analysis showed that compared with the control group (the group using western medicine alone), the experimental group (the group using xiaoqinglong decoction and sanziyangqin decoction combined with western medicine) had significantly higher overall response rate and more improved pulmonary function parameters including forced expiratory volume in the first second, forced vital capacity and percentage of peak expiratory flow, as well as significantly lower incidence rate of adverse reaction.Conclusions: Xiaoqinglong decoction and sanziyangqin decoction combined with western medicine has a significant effect in children with cough variant asthma and can reduce the occurrence of adverse reactions.

1. Introduction

Cough variant asthma (CVA) in children refers to a special type of bronchial asthma with cough as the only or main manifestation and dry cough as the main symptom without wheezing [1]. In recent years. The incidence and referral rate of children with chronic cough increase year by year, among which CVA is the primary cause of children with chronic cough [2]. Due to the lack of typical wheezing symptoms of CVA and the lack of adequate understanding of the disease by clinicians, it is often missed and misdiagnosed, which leads to the missing of the best treatment opportunity and further aggravates the condition. According to the survey, about 30% of children

can develop typical asthma [3], which has a serious impact on the child's quality of life. At the same time, chronic and frequent cough can also increase the burden on the family. At present, the treatment methods of CVA are generally anti-inflammatory, dilating the bronchi and so on.Currently, the commonly used drugs are glucocorticoids and Montelukast sodium. Although these drugs can relieve the clinical discomfort of patients to a certain extent, they are difficult to cure, and the disease is easy to repeat. In recent years, TCM treatment of CVA has increasingly become a research hotspot. Many studies have shown that TCM has significant curative effect on CVA [4-6], with little toxic and side effects. Clinical studies have confirmed that Xiaoqinglong Decoction combined with Sanzi Yangqin Decoction can effectively relieve clinical symptoms and improve lung function in patients with CVA, but there is no sufficient and reliable evidence to support this. Therefore, this study systematically searched the randomized controlled trial research literature of Xiaoqinglong Decoction combined with Sanzi Yangqin Decoction in the treatment of CVA, which was established at home and abroad and published until October 2022, aiming at systematically evaluating the efficacy and safety of Xiaoqinglong Decoction combined with Sanzi Yangqin Decoction in the treatment of CVA in children, and providing objective and powerful basis for the treatment of CVA.

2. Data and Methods

2.1. Literature Retrieval

Randomized controlled studies on Xiaoqinglong Decoction and Sanzi Yangqin Decoction in the treatment of CVA in children were collected from CNKI, WanFangData, VIP and Pubmed. The retrieval time is from the establishment of each database to October 2022. Chinese keywords is Xiaoqinglong Decoction, Sanzi Yangqin Decoction, cough variant asthma, asthma. The key words in English is "xiaoqinglongdecoction", "sanziyangqindecoction", "coughvariantasthma", "xiaobing".

2.2. Inclusion criteria

2.2.1. Type of reference

Must be a randomized controlled clinical study with or without blindness and with or without loss of follow-up.

2.2.2. Subjects

Under 14 years old, regardless of gender or race; In line with the diagnostic criteria for CVA in the Diagnostic and Prevention Guidelines for Children with Bronchial Asthma formulated by the Respiratory Group of the Pediatrics Branch of the Chinese Medical Association in 2016 [1].

2.2.3. Intervention measures

The control group was treated with conventional Western medicine (such as aerosol inhalation, oral or intravenous infusion of anti-inflammatory, spasmolytic, asthmatic, anti-infection and other drugs), and the experimental group was treated with Xiaoqinglong decoction and Sanzi Yangqin decoction plus or minus on the basis of the control group;The dosage form, dosage and course of treatment are not limited.

2.2.4. Outcome indicators

(1) In literature studies, there were description and analysis of relief of clinical symptoms such as

cough, sputum, chest tightness, duration, pulmonary rales, etc.; (2) Total effective rate; (3) Pulmonary function tests, such as forced expiratory volume in the first second (FEV1), percentage of forced expiratory volume in the first second (FEV1%), peak expiratory flow (PEF), forced vital capacity (FVC), etc.; (4) Serum levels of related inflammatory cytokines; (5) Adverse reactions.

2.3. Exclusion criteria

(1) Exclude studies that are not randomized controlled trials; (2) Excluded literature that did not indicate diagnostic criteria; (3) Excluded studies that did not meet efficacy indicators; (4) Excluded literature with repeated publication, obvious errors in data statistics and analysis, and incomplete data; (5) Excluding non-Chinese and English literature; (6) Exclusion of animal experimental research.

2.4. Literature screening and data Extraction

Literature was screened simultaneously and independently by two researchers according to inclusion and exclusion criteria. In case of disagreement, two people will decide whether to include them through discussion; If there are still any differences, they shall be settled by the third party through negotiation. After that, two researchers extracted the data of the literature respectively, and finally collated it.

2.5. Quality evaluation of the included literature

Bias risk assessment criteria proposed in CochraneHandbook 5.1.0 were used to evaluate the following indicators: random method, allocation concealment, blind method, incomplete data description, integrity of results reporting, and other potential factors affecting authenticity [7].

2.6. Statistical Analysis

Meta-analysis was performed on the data extracted from the literature using RevMan 5.4.1 software provided by the Cochrane Collaboration Network. Confidenceinterval (CI) and relative risk (OR) were effect index for binary variables. STD Mean Difference (SMD) and 95%CI were used as effect indexes for continuous variables. $P \leq 0.05$ indicated statistically significant differences. Q test and I2 test were used for the heterogeneity of the literatures. If $I2 < 50\%$ and $P > 0.1$, the heterogeneity was small, then fixed effects model was used. If $I2 \geq 50\%$ or $P < 0.1$, it indicates statistical heterogeneity, and the random effects model is used.

3. Results

3.1. Literature screening results

In order to "xiaoqinglong decoction, sanziyangqin decoction, cough variant asthma, xiaobing" as keywords retrieval of CNKI, WanFangData, VIP and Pubmed, get 142 articles. After reading the title and abstract of the article, 18 articles were obtained after excluding duplicates and literatures that did not meet the inclusion criteria. Finally, after carefully reading the full text, 14 literatures were included, all of which were in Chinese, as shown in Figure 1 and Table 1.

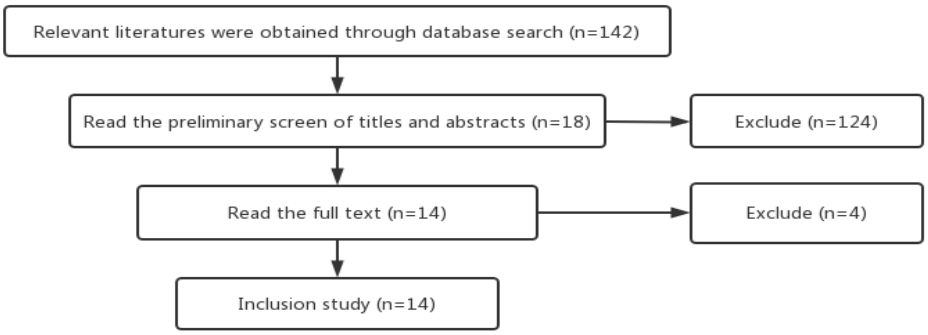

Figure 1: Literature screening flow chart

Table 1: Basic information included in the study

Inclusion study	Number of cases T/C	Intervention method		Course of treatment	Observation index
		Experimental group	Control group		
Shan Chao2015[8]	28/28	A	B	4weeks	(1)
Yu Zhiwu2016[9]	71/71	A	B	4weeks	(1)(2)(3)(7)
Chen Qiang2018[10]	30/30	A	B	2weeks	(1)(2)(3)(7)(10)
Shen Liujun2019[11]	25/25	A	B	2weeks	(1)(2)(3)(7)(10)
Wang Yongji2019[12]	44/44	A	B	4weeks	(1)
Huang Zaifeng2019[13]	41/41	A	B	2weeks	(1)
Zhao Dongyan2020[14]	60/60	A	B	1month	(2)(3)(7)
Zhang Juan2020[15]	49/49	A	B+Inhale budesonide aerosol	12weeks	(1)(2)(3)(6)
Liang Wei2020[16]	36/36	A	B	4weeks	(1)(2)(3)(7)(8)(10)
Shi Ji2021[17]	38/38	A	B	2weeks	(1)(2)(3)(7)
Hong Zhengkun2021[18]	40/40	A	B	2weeks	(1)(2)(3)(4)(9)
Yan Yili2021[19]	41/41	A	B+Inhale budesonide aerosol	4weeks	(1)(2)(3)(4)
Huang Jinbi2021[20]	81/81	A	B	8weeks	(1)(10)(11)
Fang Fang2022[21]	50/50	A	B	4weeks	(1)(2)(3)(4)(5)(6)(10)

Note: [A] Xiaoqinglong Decoction and Sanzi Yangqin decoction plus or minus+control group; [B] Montelukast Sodium Chewable Tablets; [qd] once a day; [bid] twice a day; [qih] 4 times a day. Among the observation indexes: (1) The total effective rate; (2) The forced expiratory volume of the first second (FEV1) is shown; (3) Force vital capacity (FVC); (4) Peak expiratory flow (PEF); (5) show the percentage of FEV1 in the expected value (FEV1%); (6) Ratio of FEV1 to forced vital capacity (FVC) (FEV1/FVC); (7) Expiratory flow peak percentage (PEF%= actual measured value/predicted value ×100%); (8) The levels of serum IL-4, IL-8 and TNF-α; (9) Oxygen partial pressure (PaO2); (10) Adverse reactions; (11) In terms of treatment compliance.

3.2. Literature quality evaluation

The quality of all included literatures was evaluated using the bias risk assessment criteria proposed in the CochraneHandbook 5.1.0.A total of 13 literatures [8-20] mentioned the use of random allocation method, among which 4 literatures [10,14,18,19] clearly explained the use of random number table method. One paper [13] clearly explained the implementation of double-blind method; None of the literature explicitly stated allocation hiding; All references detailed patient baseline data, treatment and outcome indicators for each group.

3.3. Outcome index analysis

3.3.1. Total effective rate

A total of 13 literatures reported Total effective rate in outcome indicators [8-14,15-21]. Among 574 patients in Xiaoqinglong Decoction and Sanzi Yangqintang group, 542 were effective. In the Western medicine treatment group, 445 of 574 patients were effective.Heterogeneity among studies P=0.99, I2=0%, indicating small heterogeneity among studies, so fixed effect model was used for analysis. The results of meta-analysis showed that the total effective rate of the experimental group was significantly higher than that of the control group, and the difference between the two groups was statistically significant (OR=5.00, 95%CI [3.32, 7.53], P<0.00001). (Figure 2)

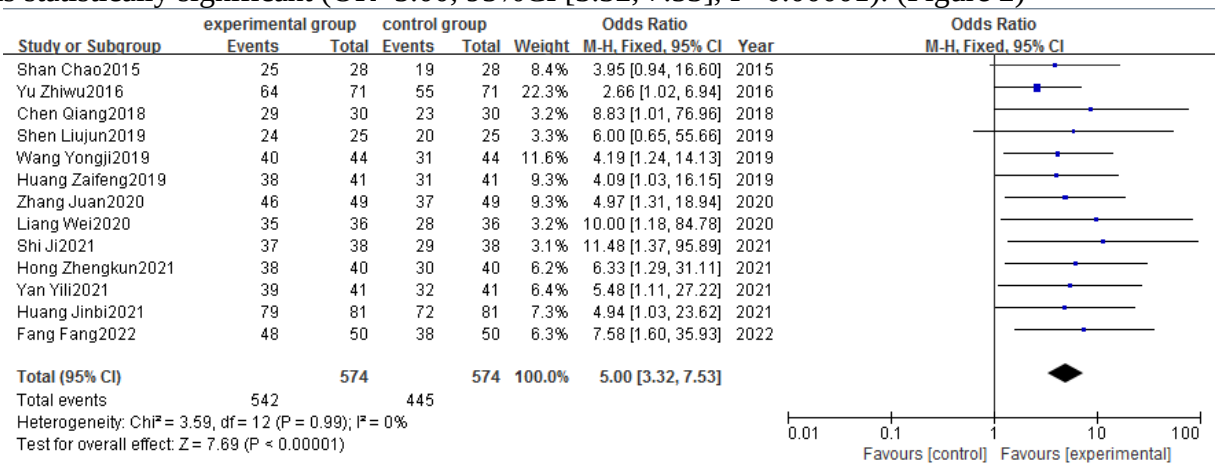

Figure 2: Meta-analysis forest map of total response rate

3.3.2. FEV1

A total of 10 literatures reported FEV1 in outcome indicators.Heterogeneity among studies P<0.00001, I2=95%, indicating heterogeneity among studies, so the random effects model was used for analysis.The results of meta-analysis showed that the improvement of FEV1 in the experimental group was significantly higher than that in the control group, and the difference between the two groups was statistically significant (SMD=1.77,95%CI[1.09,2.46],P<0.00001). (Figure 3)

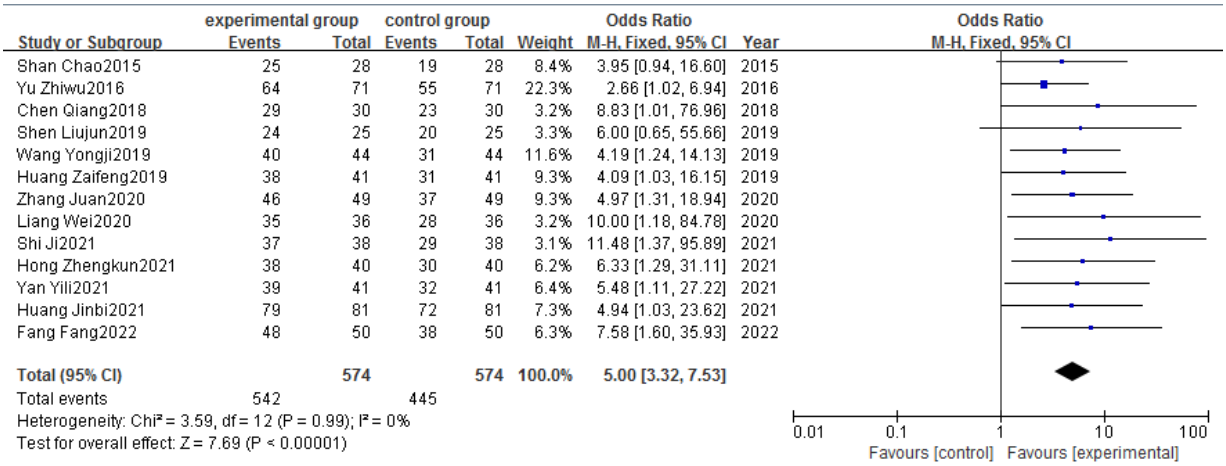

Figure 3: Forest map of meta-analysis of FEV1

3.3.3. PEF%

A total of 6 literatures reported PEF% in outcome indicators [9-11,14,16,17]. Heterogeneity among studies P=0.50, I2=0%, indicating small heterogeneity among studies, so fixed effect model was used for analysis. The results of meta-analysis showed that the improvement of PEF% in experimental group was significantly higher than that in control group, and the difference between the two groups was statistically significant (SMD=1.03, 95%CI [0.85,1.22], P<0.00001). (Figure 4)

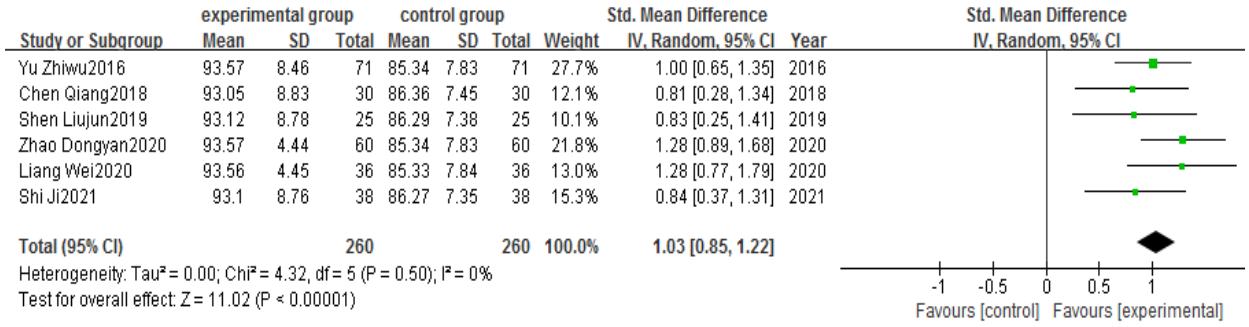

Figure 4: Meta-analysis forest map of PEF%

3.3.4 Adverse reactions

A total of 4 literatures reported adverse reactions in outcome indicators [10,11,16,20]. 15 of 172 patients in Xiaoqinglong Decoction and Sanzi Yangqintang group showed adverse reactions; Among 172 patients in the Western medicine treatment group, 43 had adverse reactions. Heterogeneity among studies P=0.29, I2=20%, indicating small heterogeneity among studies, so fixed effect model was used for analysis.Results of meta-analysis showed that the incidence of adverse reactions in experimental group was significantly lower than that in control group, and the difference between the two groups was statistically significant (OR=0.28, 95%CI [0.15, 0.54], P<0.0001). (Figure 5)

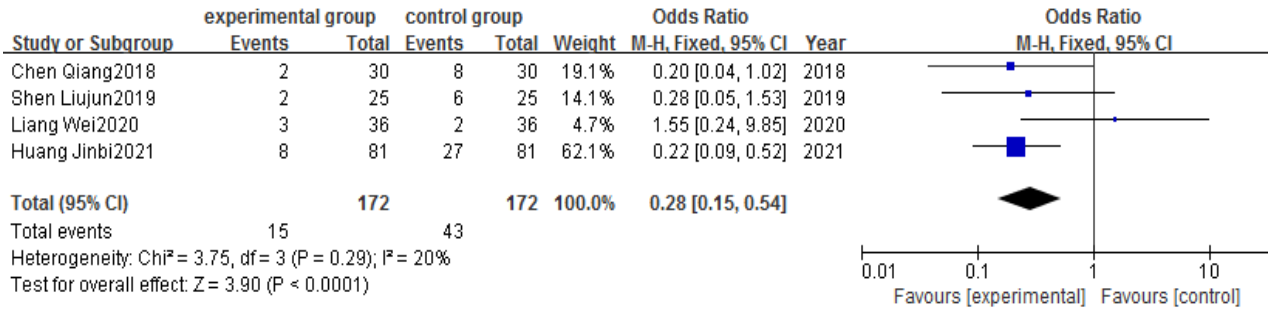

Figure 5: Forest map of meta-analysis of adverse reactions

3.4 Publication bias analysis

The publication bias funnel plot was drawn with the total effective rate as the index, and the results showed that there was a certain degree of asymmetry in the data distribution, indicating that there was a certain degree of publication bias in this study, which might be caused by the low quality of the included literature, the insufficient number of included literature and the insufficient number of research samples. (Figure 6)

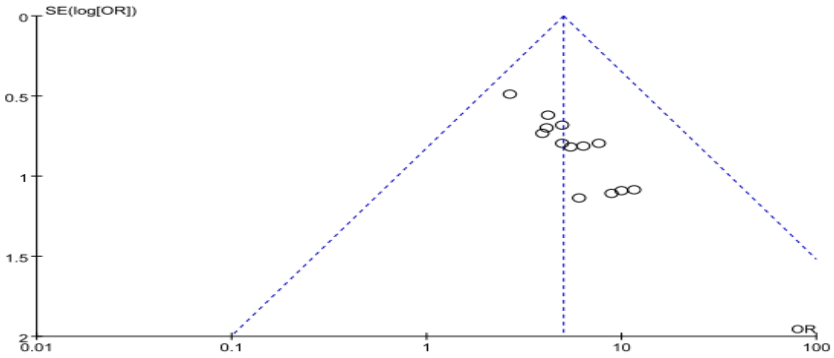

Figure 6: Funnel plot of Meta-analysis for total effective rate

4. Discussion

CVA, also known as occult asthma, is a latent form of asthma, which has a similar pathogenesis with typical asthma.Studies have shown that its etiology may be immune, genetic, environmental and other factors, and its pathogenesis is mostly related to airway inflammation, airway hyperresponsiveness and airway remodeling.

CVA also belongs to the categories of "cough" and "croup disease" in traditional Chinese medicine. Its pathogenesis is the phlegm in the lung, induced by the sensation, spittoon stroke, obstructing the airway, lung loss of xuan down. Zhu Danxi also pointed out in "Danxi heart Law" that "asthma is mainly in sputum", that the root cause of asthma attack is hidden in the lung sputum. Xiaoqinglong Decoction is composed of ephedra, cassia twig, Peony, sundried licorice, schisandra, dried ginger, asarum and pinellia. It has the effects of relieving surface and dispelling cold, warming lung and reducing cough and asthma. Sanzi Yangqin Soup is composed of Perilla seeds, white mustard seeds and semen raphani seeds. The combination of three medicines has the effect of dispelling wind, reducing phlegm and relieving cough, reducing qi, relieving asthma and dispersing knot. At present, a large number of studies have shown [22-27] that Xiaoqinglong Decoction and Sanzi Yangqin Decoction can improve the clinical symptoms of CVA and have the effects of relieving cough, asthma, expectorant, anti-inflammatory and anti-allergy. Pharmacological studies

have also found that ephedra has the effects of promoting lung, relieving asthma, improving water and anti-inflammatory [28-29]. Cassia branch has anti-inflammatory, anti-sensitization and sedative effects [30-31]. Asarum has anti-inflammatory and calming effects, relieving cough and asthma [32]. Pinellia pinellia can relieve cough, expectorant and asthmatic effects [33]. White mustard seed and semen raphani seed can relieve cough and inhibit airway hyperresponsiveness [34-35]. Perilla seed has anti-asthma and antitussive effects [36-37].

This study collected the randomized controlled trial research literature on the treatment of CVA by Xiaoqinglong Tang and Sanzi Yangqin Tang, which was published in the database until October 2022, and conducted statistical analysis, which confirmed that the treatment of CVA by Xiaoqinglong Tang and Sanzi Yangqin Tang can effectively reduce the discomfort symptoms and improve the lung function of children with CVA. It provides a scientific and objective basis for clinicians to use Xiaoqinglong Decoction and Sanzi Yangqin Decoction to treat CVA. Although the literature included in this study includes the high-quality papers recognized by the academic community since the establishment of the four major databases, due to the small number of them, the next research still needs to conduct more high-quality large-sample, multi-center, randomized controlled clinical studies for further confirmation.

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