CLINICAL RESEARCH

Systematic Evaluation (Meta-analysis) of the Efficacy and Safety of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in the Treatment of Suppurutive Tonsillitis in Children

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Supported by: National Key Research & Development Plan Project (2018YFC1707400, 2018YFC1707410); Research Funding Project For Graduate Education Teaching Reform of China Academy of Chinese Medical Sciences (JG201703)

ABSTRACT To systematically evaluate the efficacy and safety of Pudilan Xiaoyan Oral in Liquid (蒲地蓝消炎口服液) in the treatment of suppurative tonsillitis in children. In WanFang, CNKI, VIP, CBM, PubMed, Embase and Corchrane and other databases, relevant literatures about Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in the treatment of pediatric suppurative tonsillitis were searched. The retrieval time was from the establishment of the database to April 2019. Relevant randomized controlled trials were extracted. The control group was treated with conventional antibiotics, and the observation group was treated with Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) based on the control group. After they were summarized and analyzed, Cochrane Handbook 5.1 evaluation standard and RevMan 5.3 software were used to determine the quality of literature. A total of 172 literatures were retrieved and 23 randomized controlled trials were included. A total of 1188 children were in the experimental group while 1175 children were in the control group, involving 2363 children with suppurative tonsillitis. Meta-analysis showed that the total effective rate of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with routine treatment was better than that of routine treatment (RR = 0.88, 95% CI (0.86, 0.91), P<0.00001); Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with routine treatment in children was better than that of routine treatment alone in term of temperature recovery, sore throat time, the reduction of tonsil purulent secretion. There were few reports of adverse reactions and no serious adverse reactions. To sum up, Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with routine treatment can significantly improve the efficacy of children with suppurative tonsillitis, but due to the low quality of the included literature, it should be used cautiously. It is suggested that clinical randomized controlled trials should be designed with large sample size, multi-centers and conforming to international standards to improve the quality of evidence.

KEYWORDS Pudilan; Tonsillitis; Randomized controlled trials; Systematic evaluation; Meta-analysis

Acute suppurative tonsillitis[1] is a visible upper respiratory tract disease, mainly bacterial infections, and the susceptible population is children and adolescents. Acute suppurutive tonsillitis in children has an acute onset and is more frequent and more severe, and can occur in all seasons. The main clinical treatment is anti-infective therapy.

In children with acute suppurutive tonsillitis[2], the larynx nucleus on both sides of the throat (that is, the palatine tonsil) is red and swollen and painful, and the main symptoms are that it looks like a nipple or a silkworm moth. It is often called "milk moth", "rotten milk moth", and "larynx moth" in traditional Chinese medicine. The disease often repeated attacks, and is difficult to heal, becoming lesions, and causing local and systemic complications. Local complications include ear swelling, larynx palsy, and larynx etc., and systemic complications include hypothermia, palsy, palpitations, and edema etc.

Most of the milk moths are introduced into the body by unexplained external pathogen, which accumulate the lungs and stomach, or become stomach heat and toxin due to the indulgence of salty, fat and sweet food. The throat is the channel

of the lungs and stomach. The lung and stomach have accumulated heat, and they repeatly suffered from wind and heat. The channel of the lungs and stomachs is motivated for fumigation. When it is accumulated, the disease occurs.

Therefore, in *Treatise on the Origins and Manifestations of Various Diseases*, it is said that sore throats also have caused by spleen and stomach. The heat in spleen qi and stomach qi is flushed into the throat, so it causes sores. The sores are whiteheads or red roots, which are caused by pinching heat. " *The Spiritual Pivot Ulcer Chapter* said: "Heat is exuberance, meat is rot. When meat is rot, it becomes pus". This treatment of the disease is based on the principle of "clearing, eliminating, and supplementation". The principle of treatment should be to relieve heat and resolve toxins, and to relieve sore throat and swelling.

Western medicine often adopts anti-inflammatory and antiviral treatments, and antibiotics such as penicillin are widely used as the first choice for the treatment of acute tonsillitis. However, due to the irregular use of antibiotics, drug resistance is becoming more and more obvious. As reported by Cphen R, penicillin has a 35% failure rate for acute tonsillitis caused by group A hemolytic streptococcal infections, especially for children under 6 years of age.

Traditional Chinese medicine has certain advantages in treating this disease, and has achieved good curative effects. For example, LIU Yong-sheng and other studies have found that the method of clearing heat and resolve toxin, and relieve sore throat and swelling by traditional Chinese medicine, have more advantages than western medicine in the treatment of children with acute purulent tonsillitis[3]. With the inheritance and development of the medicine in China, people have expressed great hope for traditional Chinese medicine, and many treatments advocate the use of traditional Chinese medicine method and traditional Chinese medicine. Among them, for acute suppurutive tonsillitis, traditional Chinese medicine is effective, especially Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液), the main ingredients of which are *Herba Taraxacim* (Pu Gong Ying), *Herba Corydalis Bungeanae* (Ku Di Ding), *Radix Isatidis* (Ban Lan Gen), *Radix Scutellariae* (Huang Qi), etc., which can clear heat and resolve toxins, reduce swelling and expelling pus.

The systemic review of the effectiveness and safety of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in the treatment of suppurutive tonsillitis in children has been 3 years since the last review. There are few literatures and they are low in quality. This paper re-assessed the previously published clinical studies of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with antibiotics for the treatment of pediatric suppurative tonsillitis, especially those including a large number of the latest published studies in the past 3 years, with a view to providing reference for clinical practice.

MATERIALS AND METHODS

Screening Criteria

Study type: Randomized controlled trial was without language restrictions. Study subjects: Children who meet the diagnostic criteria for suppurative tonsillitis. It was with reference to the *Therapeutic Efficacy Standards for TCM Diseases and Syndromes* issued by National Administration of Traditional Chinese Medicine in January 1995:

(1) Fever, sore throat, and difficulty swallowing as the main symptoms; (2) The onset of illness is short and the course of disease is short; (3) Pharyngeal examination showed tonsil congestion, bright red or dark red, swelling, pus spots on the surface, and small abscesses in severe cases; (4) Total white blood cells and neutrophils increased. Intervention measures: The experimental group was treated with conventional treatment, and the control group was treated with conventional treatment plus Pudilan Oral Liquid (蒲地蓝口服液). Main outcome indicators: total effectiveness; secondary outcome indicators: time to return to normal body temperature, the time of throat pain disappear, the time of purulent discharge disappear from the tonsils, and adverse reactions.

Leterature Retrieval

Chinese database search by computer were as follows: WanFang database, CNKI, VIP, CBM English database: PubMed, Embase, and Corchrane. The retrieval time was from the

construction of the database until April 2019. The Chinese search term is "蒲地蓝, 扁桃体炎, 扁桃腺炎, 扁桃体发炎".

The English search term is "pudilan, amygdalitis, amygdalitis, tonsilliti". According to different databases and different retrieval methods, keywords are freely combined to search for titles, topics, abstracts, full texts, etc., and manual retrieval of related dissertations, conference papers, magazines, newspapers etc. were also searched. The publication type and the language are not limited.

Filter Literature and Extract Data

First, A total of 2 reviewers independently conducted literature screening, and the selected literatures were cross-contrasted. If there were differences, 2 people would consult the third person. Import all bibliographic titles into Note Express for screening. First, perform preliminary screening according to the established criteria for exclusion, read the title and abstract for exclusion, and then read the full text for rescreening. At the same time, the author, journal name, year, the curative effects, course of treatment, and effective outcome indicators of the experimental group and the control group were extracted and compiled into a table.

Quality Evaluation

The quality evaluation adopted the quality evaluation method recommended by Cochrane Reviewer's Handbook 5.1, including the concealment of the allocation plan; the blind method was used for the research object and the implementer of the treatment plan and the blind method was used for the measurer of the research results; the completeness of the result data; the selective reporting of the research results; Other sources of bias (e.g sample size estimates, baseline comparability). Read the full text of the study and judge the above 7 aspects based on the quality evaluation method. Finally, the literature was divided into 3 quality results: "low bias risk", "uncertainty bias risk", and "high bias risk".

Statistical Analysis

Reyman5.3 software provided by Cochrane collaboration network was used for Meta-analysis to calculate the combined effect amount. For clinically heterogeneous materia, do not easily combine effect quantities. First, search for possible heterogeneity between studies, and then perform subgroup analysis based on heterogeneity. Heterogeneity tests between studies used the I^2 test as the standard, and the size of the heterogeneity was judged according to I^2.

If I^2 < 50%, it means that the statistical heterogeneity is acceptable, and a fixed effects model were used; if $I^2 \geqslant 50\%$, it means that the statistical heterogeneity is large, and a random effect model should be used. Measurement material are expressed as Mean Difference (MD), and count materia are expressed as Relative risk (RR). Heterogeneity increased due to the different interventions used in each experimental group. Subgroup analyses were performed based on the different interventions. If the number of papers included in an outcome indicator is ⩾10, a funnel chart is needed to determine whether there is publication bias.

RESULTS

Literature Screening

A total of 52 papers were retrieved from the Wanfang database, 36 papers were retrieved from CNKI, 33 papers were retrieved from VIP, 51 paperswere retrieved from CBM, PubMed Database,

The number of documents retrieved in the Embase database and Corchrane database is 0, and there are 0 papers retrieved through other materials. A total of 172 papers are imported into Note Express for rechecking. The remaining 110 papers were read. The titles and abstracts of them were excluded from the unrelated topics. After further analysis and exclusion of the remaining 45 papers, 23 papers were finally obtained. The process is shown in Figure 1.

Basic Features of the Included Research

A total of 23 literatures were included, involving 2363 children, including 1188 cases in the test group and 1175 cases in the control group. The maximum sample size was 236 and the minimum sample size was 30. The interventions were not the same, and it was concluded that the conventional treatment can be roughly divided into Pudilan Xiaoyan Oral

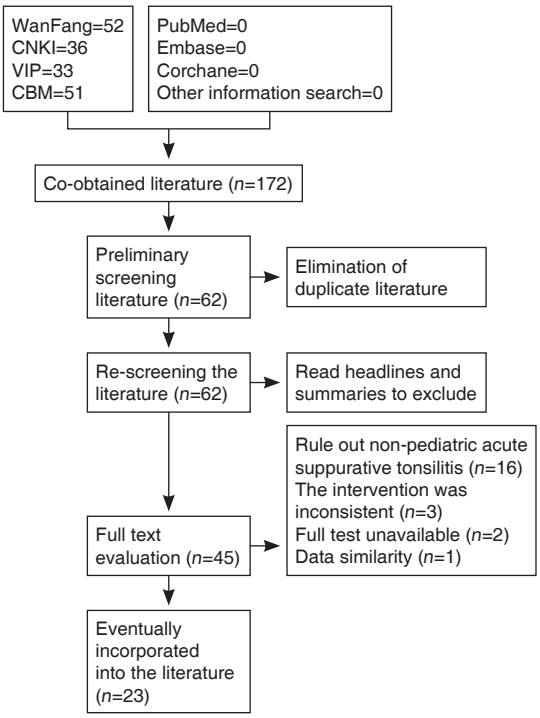

Figure 1. Flow Diagram of Study Selection

Liquid (蒲地蓝消炎口服液) + Cephalosporin vs Cephalosporin, Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) + Penicillin VS Penicillin, conventional treatment + Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) VS conventional treatment.

A total of 22 literatures reported total effectiveness and 12 studies reported adverse reactions but did not describe them in detail. There were no reports of lost follow-up and exclusion. All studies were balanced at baseline. A total of 7 studies reported the manufacturers of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液). In the included studies, the dosage and course of treatment were shown in Table 1.

Quality Evaluation of Included Studies

A total of 23 literature mentioned randomized controlled trials, of which 3 literature proposed random number table method[4.10.17], 1 literature[7]

Table 1. Basic Information of the Included Study

Author	Interventions		Course of treatment	Total number of cases	Numb-er of cases in control group	Number of cases in the test group	Outcome Indicators
	Control group	Test group					
TAN Run-guo[4] 2019	Routine therapy	Pudilan 10-20 ml + routine therapy	7 d	100	50	50	1, 2, 3, 7
FAN Chun-xin[5] 2018	Routine therapy	Pudilan 10-30ml + routine therapy	7 d	127	63	64	1, 2, 3, 6
ZHANG Xiao-dong[6] 2018	Routine therapy	Pudilan 15-30 ml + routine therapy	5 d	86	43	43	1, 2, 3, 7
LIN Yan[7] 2017	Routine therapy	Pudilan 10-30 ml + routine therapy	7 d	96	48	48	1, 2, 6
FAN Hua-dong[8] 2017	Routine therapy	Pudilan 10-30 ml + routine therapy	3 d	120	60	60	1, 2
TAN Xin[9] 2017	Routine therapy	Pudilan 15-30 ml + routine therapy	5 d	127	63	64	1, 2, 6
BU Wei-quan[10] 2016	Routine therapy	Pudilan 15-30 ml + routine therapy	5 d	160	80	80	1, 2, 3, 6
SUN Li[11] 2016	Routine therapy	Pudilan 10-30 ml + routine therapy	6 d	90	45	45	
ZHU Yan-ping[12] 2016	Routine therapy	Pudilan 10-30ml + routine therapy	5 d	120	60	60	1, 2, 7
ZHU Hui[13] 2016	Routine therapy	Pudilan 15-30 ml + routine therapy	5-8 days	80	40	40	
Mauna[14] 2015	Routine therapy	Pudilan 10-30 ml + routine therapy	7d	114	56	58	1, 2, 3, 6
JING Fang-li[15] 2015	Routine therapy	Pudilan 10-30ml + routine therapy	5–7 d	100	50	50	1, 2, 3, 6, 10
WANG Feng-zhen[16] 2014	Routine therapy	Pudilan 10-30 ml + routine therapy	7 d	30	19	20	1, 2, 3, 9
CHEN Rong[17] 2014	Routine therapy	Pudilan 10-30 ml + routine therapy	3-6 d	96	48	48	1, 2, 3, 6
PENG Er-yao[18] 2014	Routine therapy	Pudilan 10-30 ml + routine therapy	5–7 d	236	150	86	
LI Chun-ying[19] 2013	Routine therapy	Pudilan 10-30ml + routine therapy	5-7 d	100	50	50	
HUANG Jian-hong[20] 2013	Routine therapy	Pudilan 30 ml	6 d	100	50	50	1, 2, 3, 6
WANG Ying-ying[21] 2013	Routine therapy	Pudilan 10-20 ml +routine therapy	5-7 d	102	51	51	1, 2, 3, 6, 7
CHEN Shu-fang[22] 2013	Routine therapy	Pudilan 15 ml + routine therapy	5 d	98	48	50	1, 3, 4, 5
CHEN Qin[23] 2017	Routine therapy	Pudilan 10-30 ml + routine therapy	3-6 d	80	40	40	1, 3, 8
John Young[24] 2012	Routine therapy	Pudilan 15-30 ml + routine therapy	5 d	92	46	46	
ZHANG Yi-qiong[25] 2012	Routine therapy	Pudilan 10-30 ml + routine therapy	5 d	80	40	40	1, 2, 3, 6
PANG Hong-xia[26] 2011	Routine therapy	Pudilan 30 ml + routine therapy	5 d	120	60	60	1, 2, 3, 6, 7

Note: ① Time for body temperature to return to normal; ② Disappearance time of pharyngeal pain; ③ Disappearance atime of purulent secretion; ④ Blood neutrophil count; ⑤ CRP value dropped back; ⑥ Tonsillar hyperemia subsiding time; ⑦ Recovery time of mental appetite; ⑧ Time for blood picture to return to normal; Pet-name ruby hospitalization time; ⑩ Dysphagia;

mentioned odd and even random grouping. 1 literature[25] proposed coin toss randomization, and 1 literature[15] mentioned random grouping. The remaining 1 paper proposed grouping methd according to treatment method, and 1 literature mentioned average grouping.

The hidden situation of the research scheme, sample size estimation, blind implementation and random allocation scheme was not reported in all studies. A total of 12[6,10,11,16,18,23,25] studies reported the status of adverse reactions, of which 5[4,19,20,22, 23] studies reported no adverse reactions, and 7 studies proposed the content of adverse reactions; 8[4,10,11,12,21] studies reported the number of invalid cases; 1 study reported no lost follow-up and excluded cases, and the rest were reported; none of the 18 studies had a selective reporting bias, and 5 studies[4,10,11,12,21] were unclear about the existence of a selective reporting bias. The methodological quality evaluation of the included studies was performed according to the bias risk assessment tool recommended by Cochrane Handbook 5.3. The results were shown in Figure 2 and Table 2.

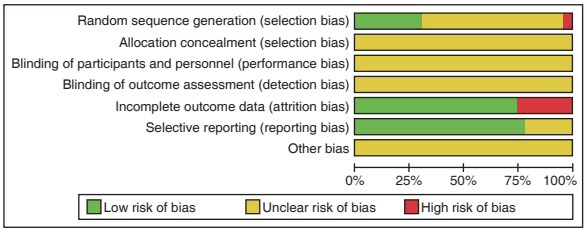

Figure 2. Percentage of Projects Included in the Study that Produced A Risk of Bias

Meta Analysis

Total effectiveness

A total of 22 studies reported the total effective rate. The dosage of one of the literature was significantly different from that of other studies. This may be the main reason for the large heterogeneity, so it was eliminated. The remaining studies had better homogeneity (I^2=35%, P=0.06). By using the fixed-effects model analysis, the overall effectiveness of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with conventional treatment was better

Table 2. Risk Assessment of Bias in Included Studies

Inclusion study	Stochastic method	Allocation Hidden	Blind method			Incomplete Data	Selectivity Results Report	Other bias
			Research Object	Tester	Outcome evaluator			
TAN Run-guo[4] 2019	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Not clear	Not clear
FAN Chun-xin[5] 2018	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
ZHANG Xiao-dong[6] 2018	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
LIN Yan[7] 2017	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
FAN Hua-dong[8] 2017	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
TAN Xin[9] 2017	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
BU Wei-quan[10] 2016	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Not clear	Not clear
SUN Li[11] 2016	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Not clear	Not clear
ZHU Yan-ping[12] 2016	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Not clear	Not clear
ZHU Hui[13] 2016	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
Mauna[14] 2015	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
JING Fang-li[15] 2015	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
WANG Feng-zhen[16] 2014	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
CHEN Rong[17] 2014	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
PENG Er-yao[18] 2014	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
LI Chun-ying[19] 2013	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
HUANG Jian-hong[20] 2013	Not clear	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear
WANG Ying-ying[21] 2013	High risk	Not clear	Not clear	Not clear	Not clear	Low risk	Not clear	Not clear
CHEN Shu-fang[22] 2013	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
CHEN Qin[23] 2017	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
John Young[24] 2012	Not clear	Not clear	Not clear	Not clear	Not clear	High risk	Low risk	Not clear
ZHANG Yi-qiong[25] 2012	Low risk	Not clear	Not clear	Not clear	Not clear	Low risk	Low risk	Not clear

than conventional treatment [RR = 0.88,95% CI (0.86, 0.91), *P*<0.00001], see Figure 4.

Secondary outcome indicator

Time to return to normal temperature

A total of 18 studies reported the time to return to normal temperature. One of the literatures was a binary variable, not a continuous variable, so it was eliminated. Therefore, a meta-analysis was performed on 17 studies; due to the different interventions in each study, the heterogeneity was too large, so the subgroup analysis was performed according to the different interventions, which were roughly divided into 4 groups.

Due to the use of different types of cephalosporins, the heterogeneity was still large when they were all divided into 1 group, so they were divided into 2 groups, namely: Pudilan + cephalosporin group 1, the heterogeneity was acceptable. By using a fixed effect model (I^2=21%, *P*=0.28), the temperature recovery time of Pudilan combined with cephalosporin treatment was longer than that of cephalosporin treatment [RR=15.58, 95% CI (15.18,15.99), *P*<0.00001]; I^2=49%, *P*=0.16, little heterogeneity, the temperature recovery time of conventional cephalosporin combined with Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) was shorter than that of conventional cephalosporin treatment [RR=24.94, 95% CI (21.01, 28.88), *P*<0.00001];

There was no heterogeneity between the studies in the Pudilan + Penicillin group (I^2=0%, *P*=0.71). Using fixed effect model results, conventional penicillin antibiotics combined with Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) for the treatment of pediatric purulent tonsillitis compared to conventional penicillin antibiotic therapy takes less time to recover body temperature [RR=30.47, 95% CI (28.49, 32.45), *P*<0.00001]; I^2=98% in Pudilan + conventional treatment group, which was statistically more heterogeneous. It was because the conventional treatment interventions in the analyzed literature were different, and similar measures cannot be found for grouping, that the differences were large. Random effect models were used in all. Meta-analysis results can be obtained [RR=18.61, 95% CI (16.52, 20.71), *P*<0.00001] see Figure 5.

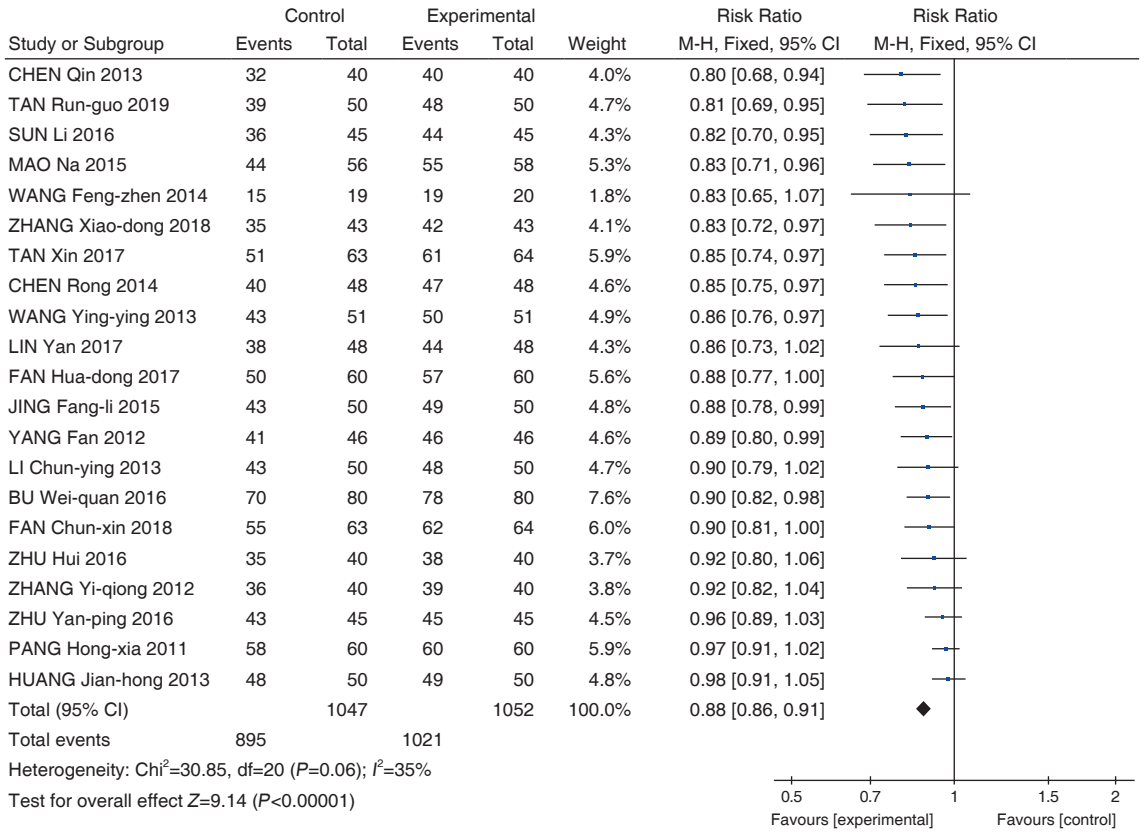

Figure 4. Total Effective Forest Map of Paodium + Conventional Treatment Versus Conventional Treatment

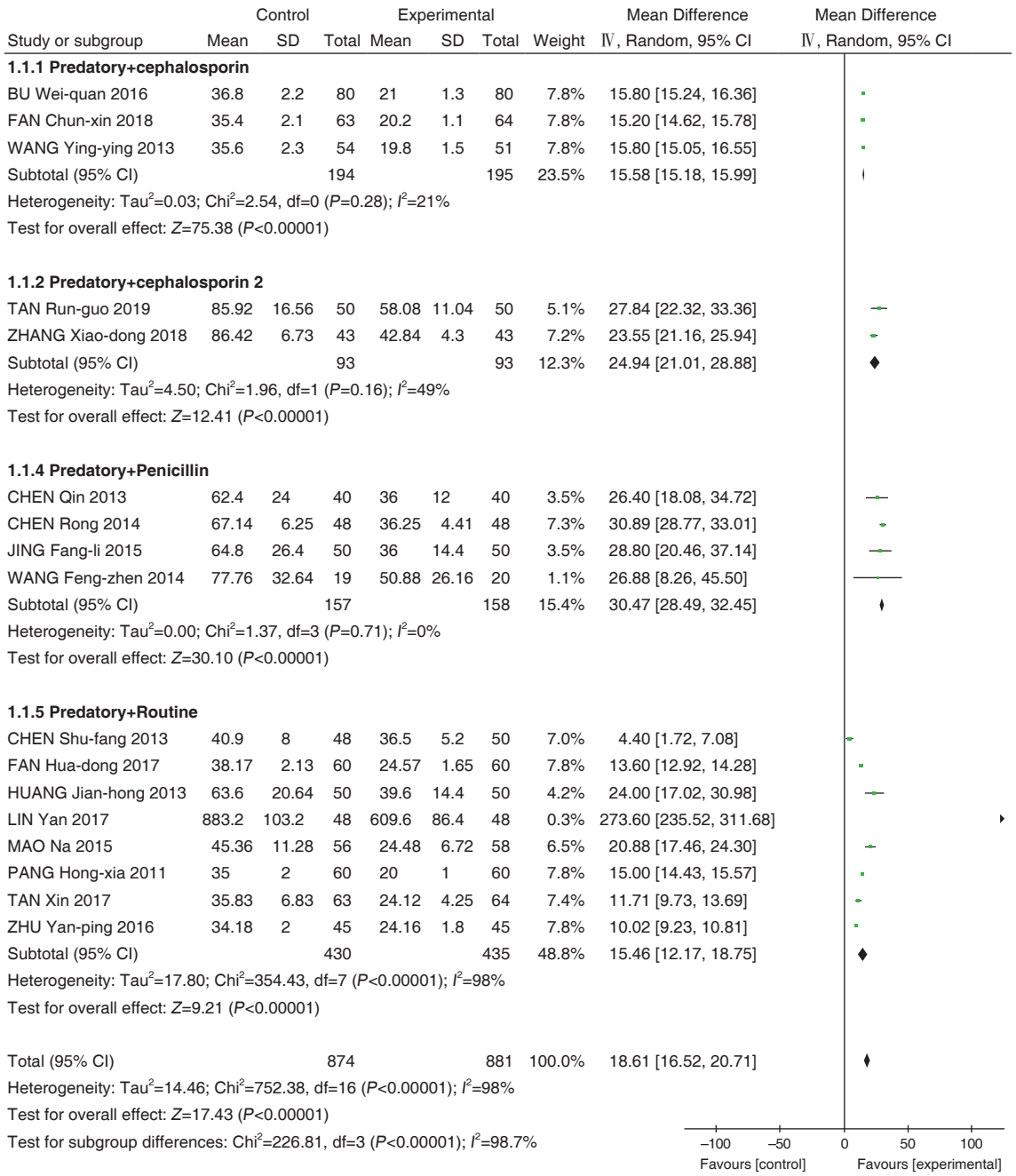

Figure 5. Predatory + Routine Treatment Contrast Routine Treatment Body Temperature Return to Normal Time Forest Map

Sore throat disappearance time

A total of 16 studies have reported the disappearance time of sore throat. According to different conventional interventions, they were divided into 3 groups for Meta-analysis. There were 834 cases in control group and 841 cases in experimental group. The groups were divided as follows: Pudilan + Cephalosporins I^2=27%, P=0.25, which meant that the statistical heterogeneity was acceptable.

Pudilan combined with cephalosporin treatment had less time to sore throat than cephalosporin treatment [RR=15.01, 95% CI (14.33,15.69), P<0.00001]; I^2=0%, P=0.55 in the Pudianlan + penicillin group. It indicated that there was no heterogeneity in statistics, [RR=32.58, 95% CI (25.77, 39.40), P<0.00001]; I^2=99% in Pudilan + conventional treatment group, statistical heterogeneity is greater. The random effect model were uniformly used, and the meta-analysis can be obtained [RR=26.13, 95% CI (21.90, 30.36), P<0.00001], see Figure 6.

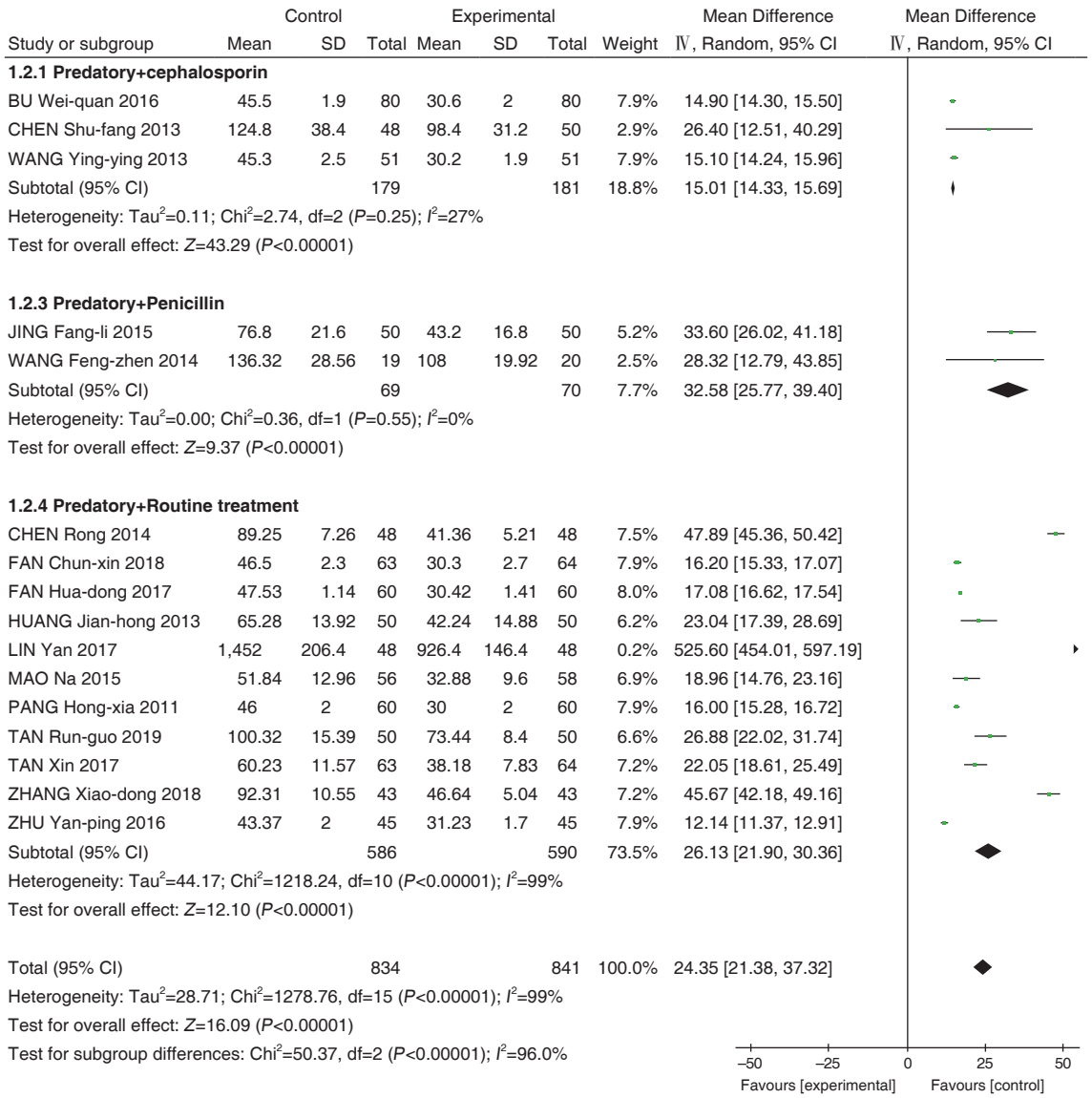

Figure 6. Forest Map of the Disappearance Time of Paodium + Conventional Treatment Versus Conventional Treatment of Pharyngeal Pain

Disappearance time of purulent secretions

A total of 13 studies reported the disappearance time of purulent secretions. Among them 1 of the literatures was a binary variable, not a continuous variable, so it was excluded. Therefore, a Meta-analysis was performed on 12 studies, including 610 cases in the control group and 614 cases in the experimental group: there was no heterogeneity in the Pudilan + cephalosporin group. I^2=0%, P=0.29, that is the result of analysis.

It is shown that the disappearance time of purulent secretion in the control group is higher than that in the experimental group [RR=13.07, 95% CI (12.44,13.70), P<0.00001]; Pudilan + cephalosporin group, I^2=9%, P=0.29, Statistical heterogeneity was acceptable, [RR=29.40,95% CI (26.80, 32.00), P<0.00001].

There was no heterogeneity in the Pudilan + penicillin group (I^2=0%, P=0.73), and the analysis result was [RR=29.90, 95% CI (27.74, 32.07), P<0.00001]; In Pudilan + conventional treatment group I^2=100%, with great heterogeneity. The random effect model was uniformly used, and the meta-analysis can be obtained [RR=18.51, 95% CI (14.68, 22.34), P<0.00001]. See Figure 7.

Adverse Reactions

A total of 12 studies recorded adverse reactions, of which 5 had no adverse reactions. In

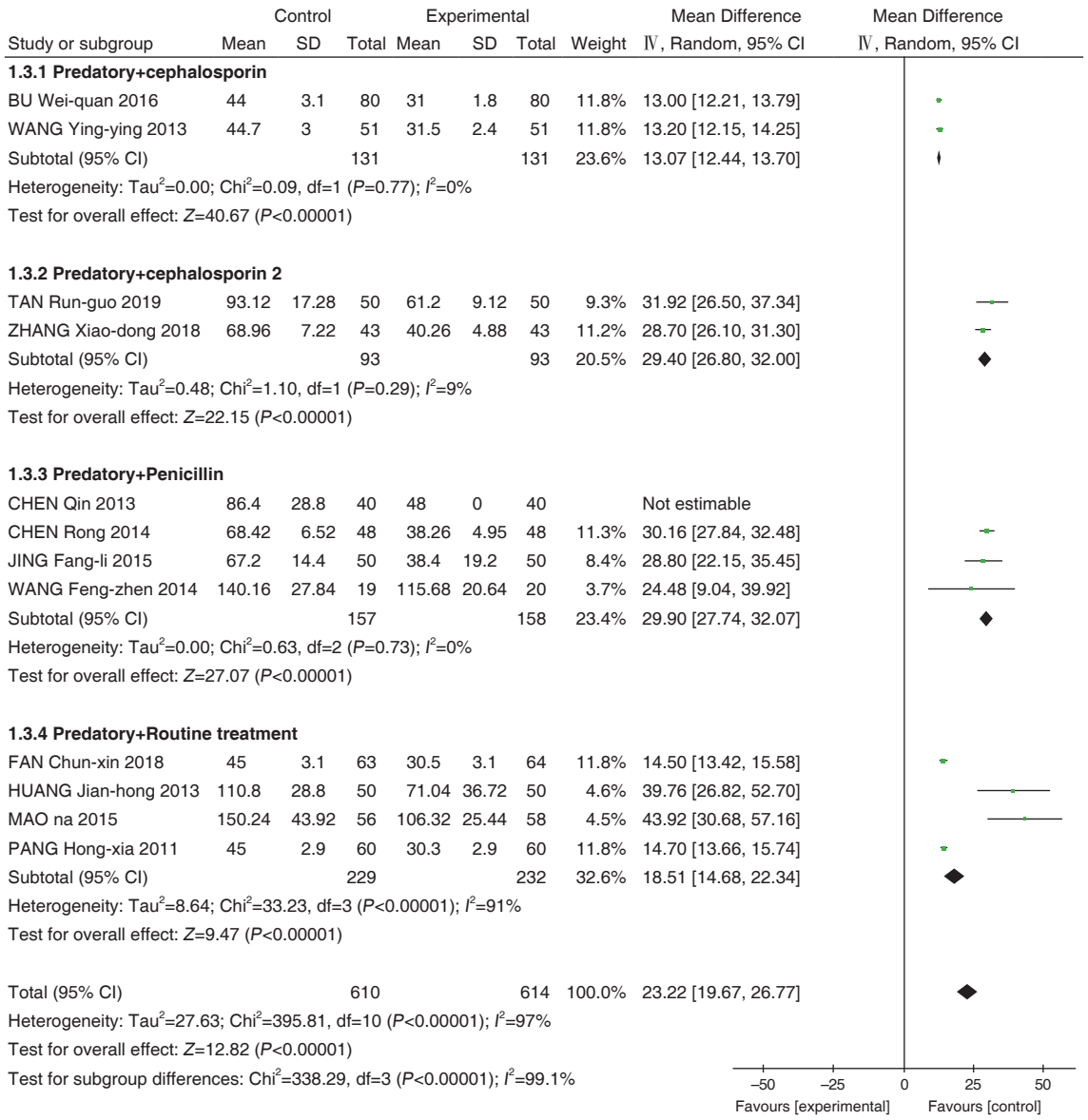

Figure 7. Forest Map of the Time of Disappearance of Purulent Secretions Compared with Routine Treatment of Pustules

5 studies, children developed diarrhea and healed after stopping the drug. In 1 study, there were oliguria, abdominal pain, arthralgia, rapid pulse, shock. All the studies indicated that the symptoms disappeared after treatment, which were considered to be related to the condition and side effects of drugs, and relatively small number of cases in the observation group. Since it cannot be determined whether it is drug-related, further research is needed to determine it. See Table 3 for details.

Publication of Bias Analysis

In this study, the secondary outcome indicators were all ⩾10. For the above outcome indicators, a funnel chart was used to analyze the publication bias, see Figure 8,9,10,11. Heterogeneity among studies was large, and heterogeneity was still large after grouping. The main reason was that the intervention measures of conventional treatment were different, and there were no uniform medications or dosages for conventional treatments in individual studies. The reasons for the bias analysis were as follows:

(1)The included studies were all in Chinese because Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) was a proprietary Traditional Chinese medicine. There was no relevant literature abroad

Table 3. Summary of Adverse Reactions

Serial Number	Research Information	Interventions		Course of treatment/day	Adverse reactions	
		Control group	Test group		Control group	Test group
1	ZHANG Xiao-dong[6] 2018	CT	PDL 15-30ml + CT	5 d	0 cases	2 cases with mild diarrhea
2	BU Wei-quan[10] 2016	CT	PDL 15-30ml + CT	5 d	Some children suffer from adverse reactions of diarrhea due to intolerance, and withdrawal of drugs can heal themselves.	
3	SUN Li[11] 2016	CT	PDL 10-30ml + CT	6 d	One case had less urine One case had abdominal pain 2 case of arthralgia 4 cases had fast pulse One case had abdominal pain 1 case of shock	One case had less urine Cases had abdominal pain Cases of arthralgia 2 cases had fast pulse Cases had abdominal pain 0 cases of shock
4	WANG Feng-zhen[16] 2014	CT	PDL 10-30ml + CT	7 d	0 cases	1 case of diarrhea
5	PENG Er-yao[18] 2014	CT	PDL 10-30ml + CT	5-7 d	None	Some had vomiting, diarrhea and body temperature fluctuation.
6	CHEN Qin[23] 2013	CT	PDL 10-30ml + CT	3-6 d days	0 cases	2 case of diarrhea
7	ZHANG Yi-qiong[25] 2012	CT	PDL 10-30ml + CT	5 d	0 cases	2 cases with mild diarrhea

Note: PDL: Pudilan Xiaoyan Oral Liquid; CT: routine therapy

and there was a language publication bias. (2) Small sample size in the study, and small samples were easy to cause publication bias; (3) Positive results were easy to publish.

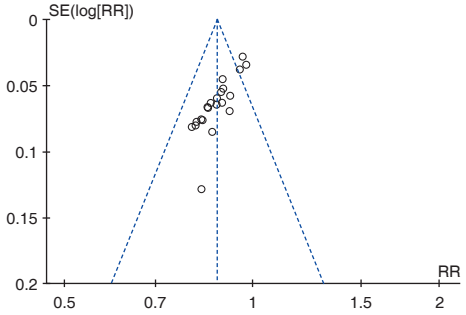

Figure 8. Total Effective Rate of Funnel Plot

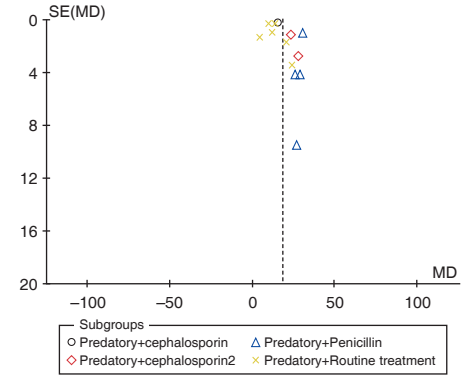

Figure 9. Temperature's Back to Normal Time Funnel Chart

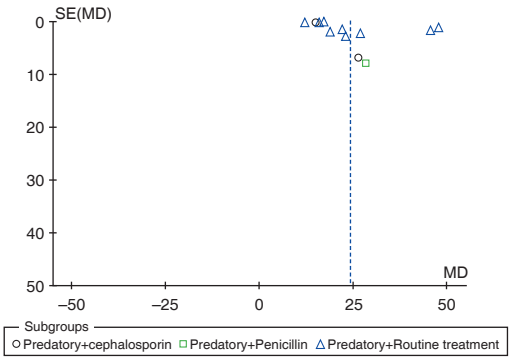

Figure 10. Time Funnel Chart of Pharyngeal Pain Disappearance Time

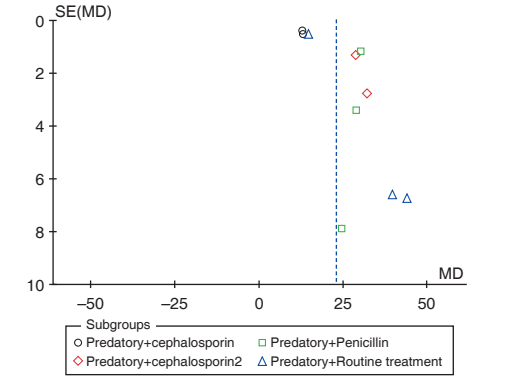

Figure 11. Disappearing Time Funnel Diagram of Purulent Secretions

DISCUSSION

Summary of Effective Evidence

Compared with the results of a systematic review of the effectiveness and safety of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) for the treatment of children with acute suppurative tonsillitis, the results reported in this study were similar to those reported in the total effective rate,

temperature recovery time, and tonsil secretion disappearance time. But this study increased the number of literature included in the analysis of adverse reactions, the disappearance of sore throat, and a more comprehensive and systematic analysis of the effectiveness of the safety box of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) for treating children with acute suppurative tonsillitis.

This study comprehensively searched Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) for the treatment of pediatric acute suppurative tonsillitis, excluding studies containing other traditional Chinese medicine and traditional Chinese medicine interventions based on the total effectiveness of all literature records, and the secondary outcome indicators according to the intervention different subgroup analysis. The final analysis obtained for effectiveness of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in the treatment of suppurutive tonsillitis in children.

From the results of the Meta-analysis, it can be seen that the duration of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with cephalosporin and penicillin in the treatment of pyogenic tonsillitis in children was shorter than that of conventional antibiotics in the case of consistent efficacy standards. For those with greater heterogeneity by Meta-analysis, descriptive analysis was performed and RevMan software was used to analyze and compare the original data provided by the study. However, as the sample size was too small and not representative, the quality was generally not high, and the interventions were more complex and diverse. Those affected the reliability of the conclusions. Further research was needed to confirm it by using large samples, multiple centers, and sufficient follow-up randomized controlled trials.

Summary of Safety Evidence

At present, Chinese patent medicine was now more and more widely used in clinical practice. Compared with traditional Chinese medicine and Western medicine, Chinese patent medicine was more convenient, fast and effective. However, as Chinese patent medicines were extracted from various active ingredients of traditional Chinese medicines, it was easy to stimulate the body to produce a pathological immune response. More attention should be paid to its safety. The dosage of the medicines included in this study was increased according to the age of the children, which basically met the instructions of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) (Oral, 10 ml once, 3 times a day, reduce it with children).

They were all produced by Jiangsu Jichuan Pharmaceutical Co., Ltd. From the perspective of literature existing, there were fewer records of adverse reactions, and they could heal themselves after discontinuation. Most of the reported adverse reactions were diarrhea, but all literature has not reported specific research information, such as the adverse reaction rate, the combination of drugs, whether it was related to the disease, so the safety needs to be further studied and clarified.

It is recommended to improve the relevant information, such as the instructions, especially the usage and dosage, and indicate the effective dose for clinical use according to the age, weight, and condition of the child; specifically recorded the clinical manifestations and the use of combined drugs to distinguish disease symptoms and adverse reactions; in order to study whether it was drug-related.

Methodological Quality of Research

Conventional treatments were different in all the studies. Although heterogeneity analysis was performed, the differences were still large and may affect the results of the study. Methodological quality evaluation includes the implementation of randomization schemes, the use of blind methods, and sample size estimation. The included studies have the following problems:

(1) Random methods were more general among studies. Although random grouping was mentioned, random planning and implementation were not described in detail. (2) All studies do not mention allocation concealment, which was to ensure that patients have equal opportunities to enter the treatment group or control group, to prevent selective bias, and to keep the allocation sequence strictly confidential before allocation to

ensure the success of the allocation sequence.

Insufficient or incomplete trials compared with trials in which the authors reported adequate allocation of concealment, the former had higher estimates of treatment effect than the latter. These results provided strong empirical evidence that inadequate allocation concealment can lead to bias in assessing treatment effectiveness. (3) The blind method was intended to prevent implementation bias and measurement bias. In confidential allocation sequence after allocation, all studies have not mentioned the blind method, which was an uncertainty judgment criterion for bias risk. There were certain difficulties in implementation; (4) The sample size of the study was small, cannot accurately reflect the curative effect, and is prone to deviation;

Clinical Significance and Outlook

Meta results showed that Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with conventional treatment can improve the effectiveness of the treatment of pyogenic tonsillitis in children, shorten the time for children's body temperature to return to normal, shorten the disappearance time of tonsill purulent secretions, and reduce the disappearance time of sore throat time, tonsil enlargement or congestion resolution time.

In summary, in order to produce high-quality evidence to provide strong evidence to support the application of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in clinical practice, the following points were suggested in future clinical research: (1) disease standardization: first in the design stage of the scheme, strict inclusion and exclusion criteria should be set in accordance with the latest diagnostic guidelines, and the dialectics of diseases should be with integrative Chinese and Western medicine, including dialectical classification of TCM and diagnosis of Western medicine, in order to obtain a recognized effect evaluation; (2) Adverse events should be carefully recorded: Adverse events were also important indicators for determining the efficacy of the drug, extending follow-up time, recording shedding and loss of follow-up, and reporting important outcomes of long-term observation; (3) Recording combined medication: due to different clinical symptoms in different children, the combined medications used were different. In order to reduce the risk of bias, the combined medications were recorded for further statistical analysis in the future. (4) Specific random methods were detailed: Randomized controlled trials are the gold standard for clinical research. Random schemes are designed in advance and were strictly followed. The implementation of a random plan ensures that the randomized trials were carried out effectively.

CONCLUSION

Based on the existing data and methods, it was proved that Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) combined with conventional treatment can improve the total effective rate, shorten the disappearance time of children's clinical symptoms, without serious adverse reactions. However, the overall quality of the included studies is not high, so the results of the study need to be further verified. More large samples, multiple centers, and rigorous randomized controlled trials were needed to study the efficacy and safety of Pudilan Xiaoyan Oral Liquid (蒲地蓝消炎口服液) in the treatment of pyogenic tonsillitis in children, with a view to providing higher evidence-based evidence for its clinical use.

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(Received Octorber 5, 2019)