

Original Research Article

Comparative effectiveness and safety of xiyanping with ribavirin for rotavirus enteritis therapy in childhood: A systematic review and meta-analysis

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Abstract

Purpose: To employ meta-analysis to assess the effectiveness and adverse events of Xiyanping and ribavirin in children with rotavirus enteritis.

Methods: Searches included PubMed, Embase, Medline, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine Database (CBM), China Science and Technology Journal Database (VIP database), and Wanfang database from inception to March 2017. Clinical indicators, with respect to the total effectiveness rate, fever time, duration of diarrhea, creatinine kinase MB isoenzyme (CK-MB), rotavirus (RV) negative conversion rate, and adverse reaction, were compared between Xiyanping and ribavirin groups.

Results: Five-hundred and twenty-six records were obtained after searching the databases, and 18 studies (3557 participants) that met the inclusion criteria were included. All of them assessed total effectiveness rate, and two records evaluated RV negative conversion rate. There were significantly higher rates in the Xiyanping group than in the ribavirin group {OR = 3.76, 95 %CI (3.03 - 4.66), $p < 0.00001$; OR = 2.68, 95 %CI (1.56 - 4.60), $p = 0.0004$ }. Compared with ribavirin group, fever time, duration of diarrhea, and creatine kinase isoenzyme MB (CK-MB) were significantly lower in xiyanping group [MD = -1.23, 95 %CI (-1.64 to -0.81), $p < 0.00001$; MD = -2.15, 95 %CI (-2.68 to -1.62), $p < 0.00001$; MD = -16.90, 95 %CI (-17.23 to -16.57), $p < 0.00001$ }. Six studies reported adverse reactions, but there was no significant difference between xiyanping and ribavirin groups {OR = 1.44, 95 %CI (0.40 - 5.17), $p = 0.58$ }.

Conclusion: This review suggests that xiyanping is more effective than ribavirin in children suffering from rotavirus enteritis.

Keywords: Ribavirin, Rotavirus enteritis, Systematic review, Virazole®, Xiyanping

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INTRODUCTION

Rotavirus (RV) causes acute vomiting, diarrhea, and fever, and is a major cause of enteritis in infants and children younger than 5 years of age, with an estimated 2 million hospitalizations and 450,000 to 700,000 deaths worldwide per year [1]. RV was discovered in 1973 and is the main pathogen in infantile diarrhea in developing countries [2]. Rotavirus enteritis often occurs in autumn and winter in China [2]. The highest RV infection rate occurs in children at the age of 3 to 5 y, and the greatest risk for developing severe disease that may negatively affect the respiratory system, myocardium, liver, kidneys, and nervous system occurs between 6 to 24 months of age [3,4]. In clinical settings, the treatment of rotavirus enteritis usually consists of dietary guidance, intestinal mucosa protector, microecological agents, and fluid therapy according to the situation, and may include cardiogenic, liver-protecting, cough-relieving, and sputum-reducing measures. There are no unique antiviral drugs for RV enteritis in China, and ribavirin and Xiyanning injections are usually used. Xiyanning is a preparation derived from the herb *Andrographis paniculata* that is a water-soluble extract containing the bitter principle andrographolide, which is a primary labdane diterpenoid. Xiyanning has been used in China for many years, as it possesses antibacterial, anti-inflammatory, and antiviral activities [5, 6]. Therefore, to derive a more precise evaluation on the effectiveness of ribavirin and Xiyanning in patients with rotavirus enteritis, a meta-analysis was performed.

METHODS

Search strategy

We undertook searches in order to identify relevant studies in the following databases: PubMed, Embase, Medline, the Cochrane library, CBM, CNKI, WanFang Database, and VIP Database. Searches for keywords included Xiyanning, andrographolide sulfonates, ribavirin, Virazole®, rotavirus enteritis, RV, and autumn diarrhea.

Inclusion and exclusion criteria

The following criteria had to be met in this meta-analysis: (1) age range between 28 days and 18 y; (2) randomized controlled trials (RCTs); (3) all subjects with rotavirus enteritis should fulfill the standard accepted diagnostic criteria with RV-positive cases [7]; (4) two groups treated by Xiyanning or ribavirin (Xiyanning vs ribavirin) and the duration of medication above three days; (5)

the outcome included the total effectiveness rate, fever time, duration of diarrhea, creatinine kinase MB isoenzyme (CK-MB), RV-negative conversion rate, or adverse reaction. Non-RCT studies, RV-negative or undetected studies, reviews of full text, conference abstracts, those with insufficient data for detailed analysis, and groups combined with other drugs, which influenced the results, were excluded.

Selection of studies

Liu and Jia independently screened each title and abstract of all retrieved studies meeting the inclusion criteria. A study was excluded when it did not relate to randomized controlled trials for pharmacological treatment of rotavirus enteritis in children and infants older than 28 days. Discrepancies were resolved by consensus; otherwise by the third author, Wang.

Data extraction and management

Liu and Wang separately extracted data from each included RCT using a data extraction form including the first author's name and publication year, patients' information, therapeutic methods and dosage, and the outcome measurements of interest. These data were entered into the Revman 5.3 software. In cases of disagreement, the third author Jia was consulted.

Statistical analysis

Cochrane Revman 5.3 software was employed for data analysis. For meta-analyses of dichotomous outcomes, dichotomous and continuous outcomes are presented as odds ratios (ORs) and standardized mean difference (SMD). $I^2 > 50\%$ denotes significant heterogeneity [8]. The fixed-effect model was used when $I^2 < 50\%$. If the calculated I^2 was greater than 50%, random-effect and fixed-effect models were compared for pooled estimates.

RESULTS

Search results and study characteristics

On account of duplicate publication, non-RCTs, RV negative or undetected, or without included criteria, reviews, and conferences abstracts, 508 studies were excluded and 18 studies were included (Figure 1). Among the included studies, 18 studies [9-26] reported the total effectiveness rate, four studies [11,14,20,25] evaluated fever time, 4 studies [10,11,14,20] related the duration of diarrhea, 3 studies [13,17,22] reported CK-MB, 2 studies were related to the RV-negative conversion rate (RSV) [17,22], and six studies

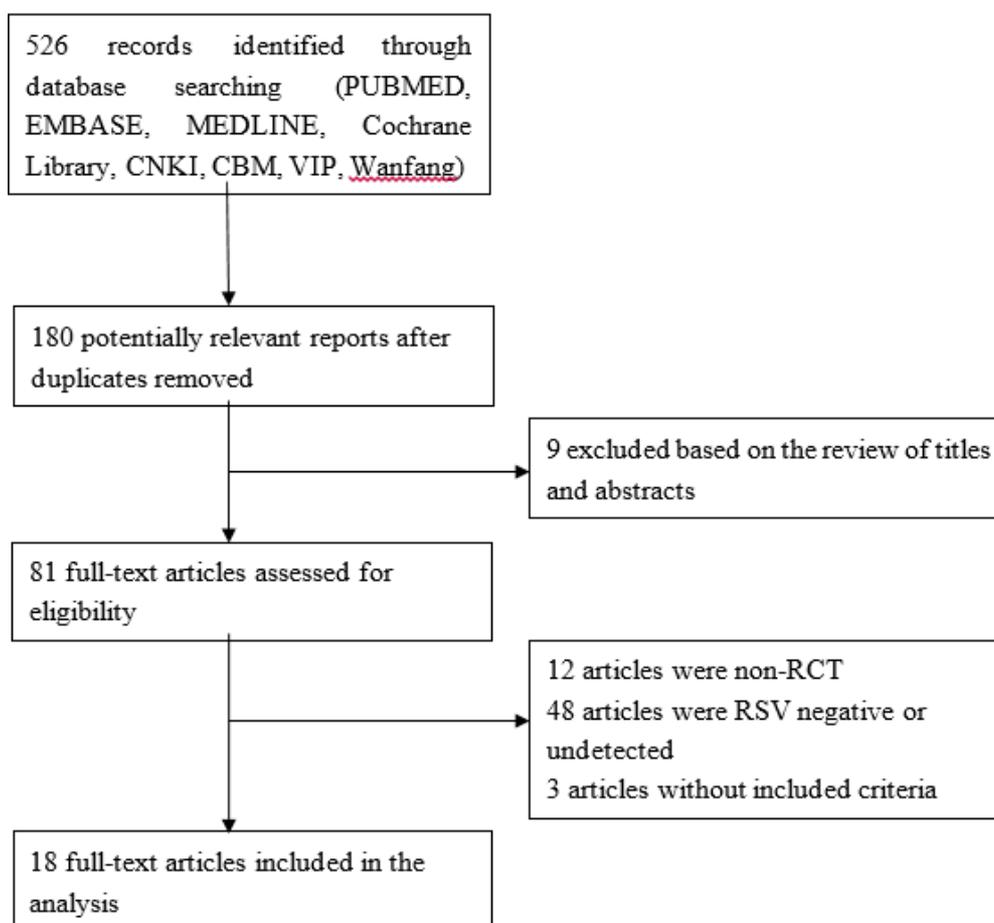


Figure 1: Study flow

[11,14,19-21,26] described adverse reactions. The basic characteristics of the selected studies are summarized in Table 1.

Risk of bias in included studies

Assigning categories of high risk/ unclear risk/ low risk are presented in Figure 2A and Figure 2B for each included studies.

Total effectiveness rate

Eighteen articles, without significant heterogeneity ($I^2 = 0\%$), reported the total effectiveness rate (Figure 3A), and were analyzed by the fixed-effect model. The xiyanning group was significantly higher than the ribavirin group $\{OR=3.76, 95\% CI (3.03-4.66); Z=12.06, p < 0.00001; Figure 3A\}$ in the total effectiveness rate.

Fever time and duration of diarrhea

The fever time and duration of diarrhea in the Xiyanning group were significantly lower as compared to the ribavirin group $[MD= -1.23, 95\% CI (-1.64\sim-0.81); Z=5.80, p<0.00001$ and

$MD= -2.15, 95\%CI (-2.68\sim -1.62); Z=7.98, p<0.00001; Figure3B$ and Figure 3C). The random-effect model was used because there was marked heterogeneity among the studies above.

CK-MB and RV-negative conversion rate

Xiyanning obviously decreased the value of CK-MB compared with ribavirin $\{MD=-16.90, 95\%CI (-17.23\sim -16.57); Z=100.98, p<0.00001; Figure4A\}$, with low heterogeneity ($p = 0.57, I^2 = 0\%$). Two articles reported the RV-negative conversion rate, and the Xiyanning group was significantly higher than the ribavirin group $\{OR=2.68, 95\%CI (1.56\sim 4.60); Z=3.57, p=0.0004; Figure4B\}$; these articles were analyzed by the fixed-effect model for lacking heterogeneity.

Adverse reaction

Six studies, without heterogeneity [$p = 0.91, I^2 = 0\%$], reported the adverse reaction of Xiyanning and ribavirin in rotavirus enteritis, and were analyzed by the fixed-effect model. There were no adverse reactions in four of them, whereas

Table 1: Baseline characteristics of included studies

| Study | Cases (T/C) | Intervention | Outcome indicator |
|--------------------------|-------------|---|---------------------|
| Chen, (2011) [10] | 36/32 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) (3) |
| Chen, (2015) [14] | 60/60 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (2) (3) (6) |
| Deng, (2014) [15] | 40/40 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (3) |
| Huang, (2017) [11] | 50/50 | T: Xiyanning injection, IV, 10mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) (2) (3) (4) (6) |
| Jiang, (2013) [9] | 960/880 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) |
| Liu, (2004) [16] | 74/48 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) |
| Liu, (2008) [12] | 35/35 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 5-10mg/(mg-d) once daily | (1) |
| Shi, (2011) [13] | 40/40 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (4) |
| Xu, (2012) [17] | 47/54 | T: Xiyanning injection, IV, 7.5mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) (4) (5) |
| Zeng, (2012) [18] | 45/45 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) |
| Zhang, (2011) [19] | 40/40 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 5-10mg/(mg-d) once daily | (1) (6) |
| Zhang, (2013) [20] | 170/90 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) (2) (3) (6) |
| Zhang, (2014) [21] | 37/35 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (6) |
| Zhaoqing, (2015) [22] | 68/60 | T: Xiyanning injection, IV, 7.5mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) (4) (5) |
| Zhaoxiaoyan, (2015) [23] | 21/21 | T: Xiyanning injection, IV, 5mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) |
| Zhong, (2009) [24] | 48/40 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10mg/(mg-d) once daily | (1) |
| Zhou, (2012) [25] | 60/60 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (2) |
| Zhou, (2013) [26] | 48/48 | T: Xiyanning injection, IV, 5-10mg/(mg-d) once daily C: Ribavirin injection, IV, 10-15mg/(mg-d) once daily | (1) (6) |

Note: (1) The total effectiveness rate; (2) Fever time; (3) Duration of diarrhea; (4) CK-MB; (5) RV-negative conversion rate; (6) Adverse reaction

skin rashes, leukopenia, and diarrhea were reported in the other two studies. The results indicate that skin rashes, leukopenia, and diarrhea symptoms were without significant difference in the two groups {OR=1.44, 95%CI (0.40~5.17); Z=0.56, P=0.58; Figure 4C}.

Publication bias

Publication bias is graphically represented by funnel plots in Figure 5, which shows no publication bias in these studies.

DISCUSSION

The main ingredient of Xiyanning is andrographolide, a diterpenoid lactone from *Andrographis paniculata*, which is a traditional

medicinal herb of the *Acanthaceae* family that has been widely cultivated in China, India, Thailand, and other Asian countries for centuries. Andrographolide is well known for its anti-inflammatory effects under various conditions such as cancer and malaria, its antiviral action against infections of the upper respiratory tract and intestinal tract, and its immunomodulatory effects whereby it enhances the expression of cytotoxic T cells and natural killer cells and promotes phagocytosis and antibody-dependent cell-mediated cytotoxicity [27-31].

Andrographolide showed potential antibacterial activity against most Gram-positive bacteria and Gram-negative bacteria, such as *Staphylococcus aureus*, *Streptococcus*

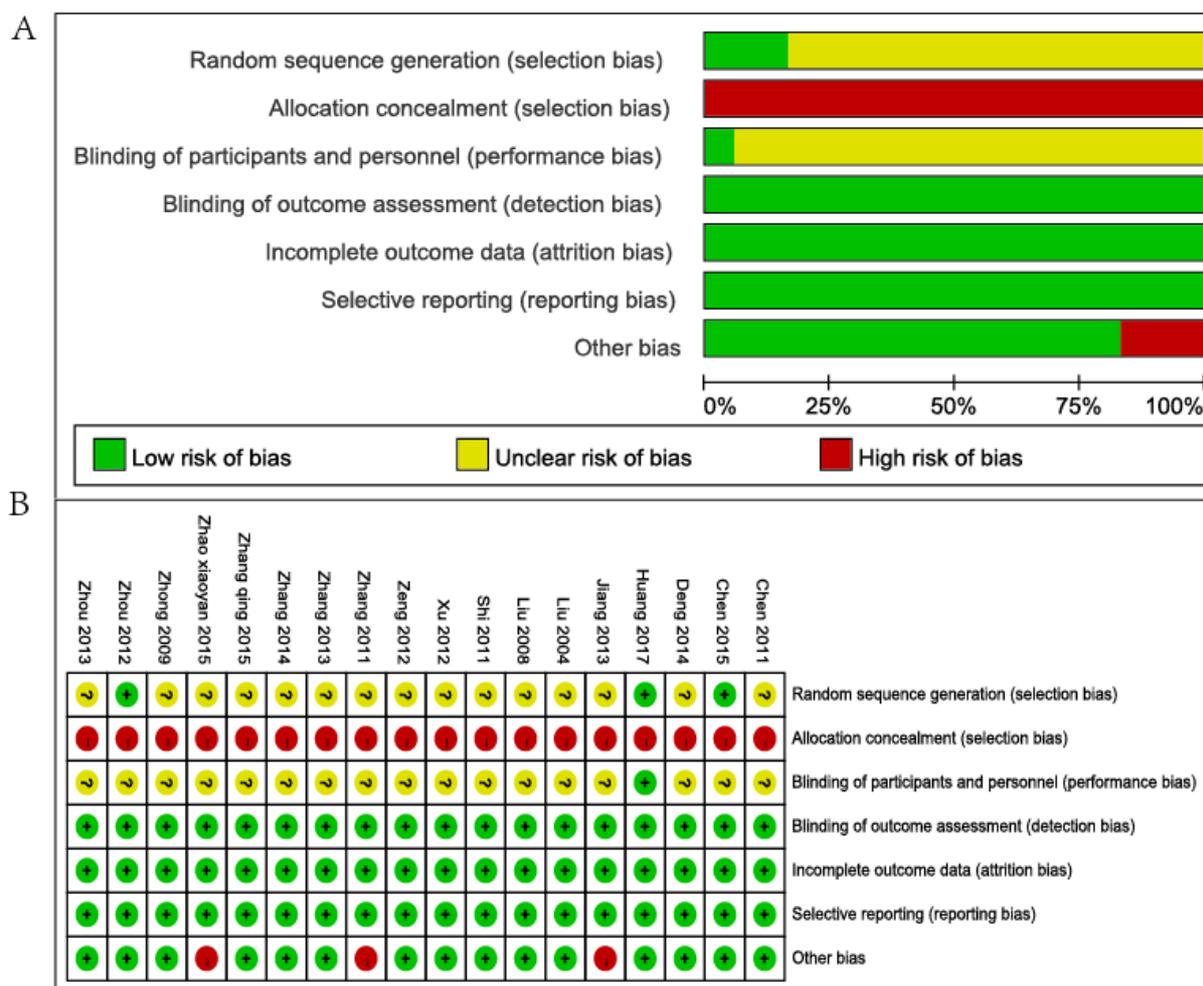


Figure 2: A = risk of bias graph: each risk of bias item presented as percentages across all included studies. B = risk of bias summary: each risk of bias item for each included studies

pneumonia, and *Escherichia coli* [31]. Apart from its antibacterial activity, andrographolide can inhibit viral replication and induce viral destruction in pathogens such as influenza A virus (IAV), hepatitis virus, herpes simplex virus (HSV), Epstein-Barr virus (EBV), human papillomavirus (HPV) [28]. Seubsasana *et al* showed that andrographolide exhibits anti-replication activity and decreases the expression of gpC and gpD throughout treatment, although it was able to inhibit HSV entry by less than 50 % [32]. Chang *et al* [33] found that andrographolide cannot directly inhibit viruses, but inhibits virus-induced cell signaling dysregulation, which results in an increase in CD4⁺ lymphocytes [33].

In this systematic review, we reviewed the data from 18 comparisons, involving 3557 patients with rotavirus enteritis, and we made several important observations. The major findings of this meta-analysis are that the total effectiveness rate was significantly higher for Xiyanning as compared to ribavirin. The study suggested that

Xiyanning shortens the fever time and duration of diarrhea, lowers the value of CK-MB, and increases the RV-negative conversion rate compared with ribavirin. In addition, adverse reactions were equal in the two groups.

One meta-analysis found that Xiyanning was equally effective as ribavirin in the treatment of patients with RV enteritis [3]. However, those authors searched from January 2003 to December 2013 in four databases and only one outcome indicator. Therefore, the article analyzed published RCTs to evaluate the role of Xiyanning in RV enteritis, comparing the efficacy and safety with ribavirin. No publication bias existed among the studies according to the funnel plot.

Study limitations

The current study has the following limitations. Firstly, the quality of the studies was not high, and the participants were all Chinese. There was

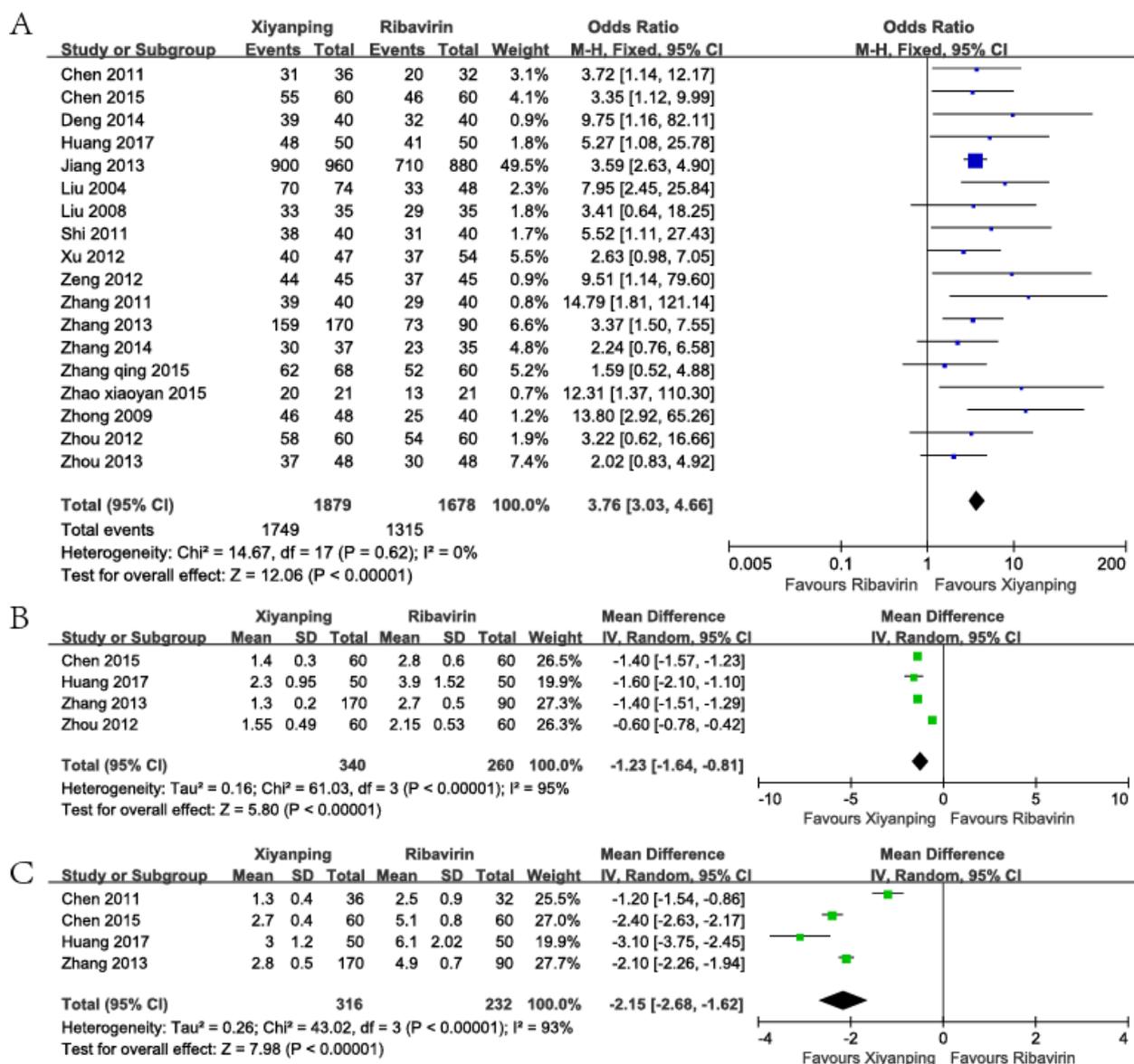


Figure 3: Forest plot of comparison of the total effectiveness rate (A), the fever time (B), and diarrhea duration (C) of Xiyanning versus ribavirin in rotavirus enteritis

a lack of other high-quality studies in other languages and a lack of multi-center randomized clinical trials. In future research, it is necessary that the efficacy and safety of Xiyanning be proven in other races. Secondly, only three articles described the random methods used, and one mentioned blindness but without methodology, but no trial explained the allocation concealment method. Finally, we have not yet analyzed reasons, why the heterogeneity of Figure 3B reduced to 0% when the study by Zhou in 2012 was removed. Thus, the random-effect model was selected. Future research should focus on the limitations of the above issues.

CONCLUSION

This review suggests that Xiyanning is more effective than ribavirin for RV enteritis, based on the included RCTs. The antiviral activity of andrographolide has been demonstrated in many virus infections, and thus has the potential for being developed as a new highly potent antiviral drug with multiple effects. However, further analyses with larger samples and other races are needed to confirm the efficacy and safety of Xiyanning for rotavirus enteritis in childhood.

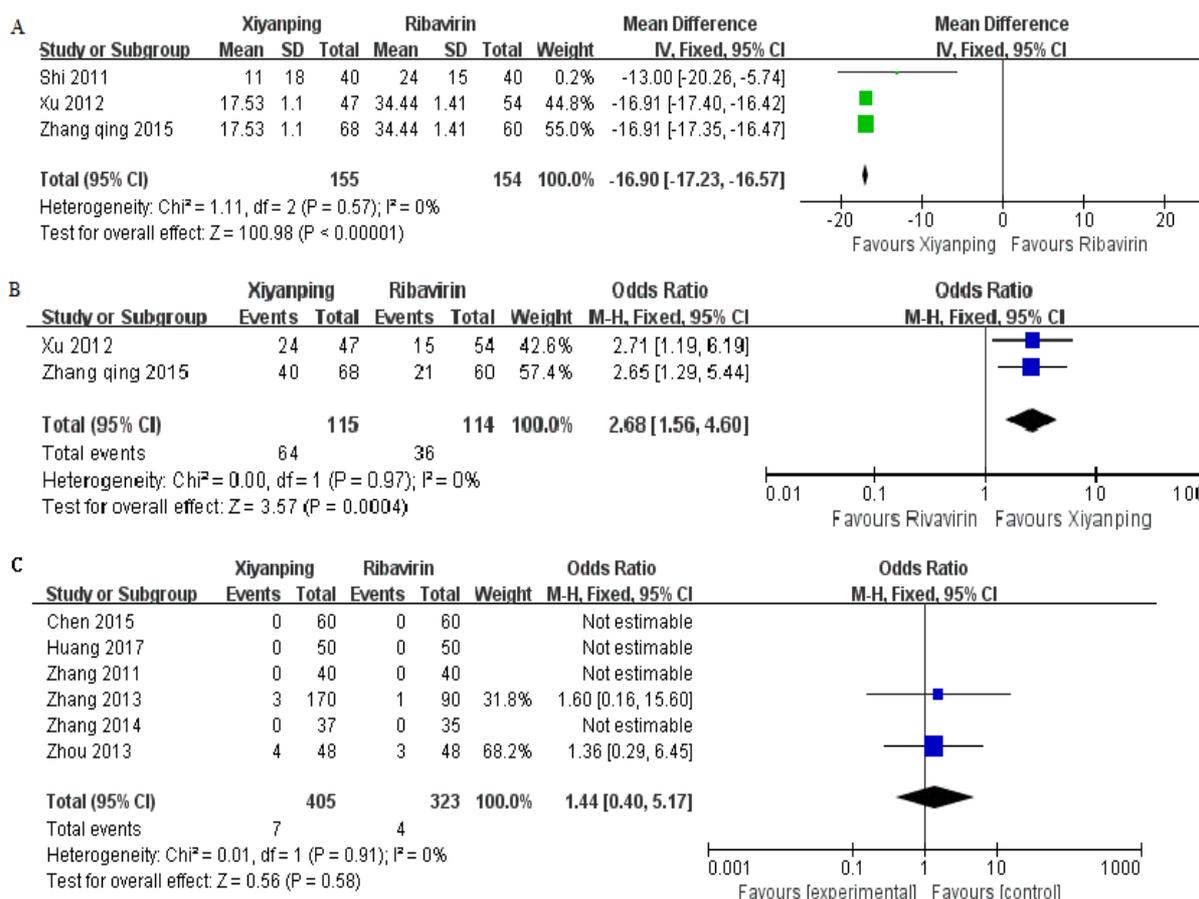


Fig. 4 Forest plot of comparison CK-MB (A) and RSV negative (B) and the Adverse Reaction (C) of Xiyanning versus ribavirin in rotavirus enteritis

Figure 4: Forest plot of comparison of CK-MB (A), RV-negative (B), and the adverse reaction (C) of Xiyanning versus ribavirin in rotavirus enteritis

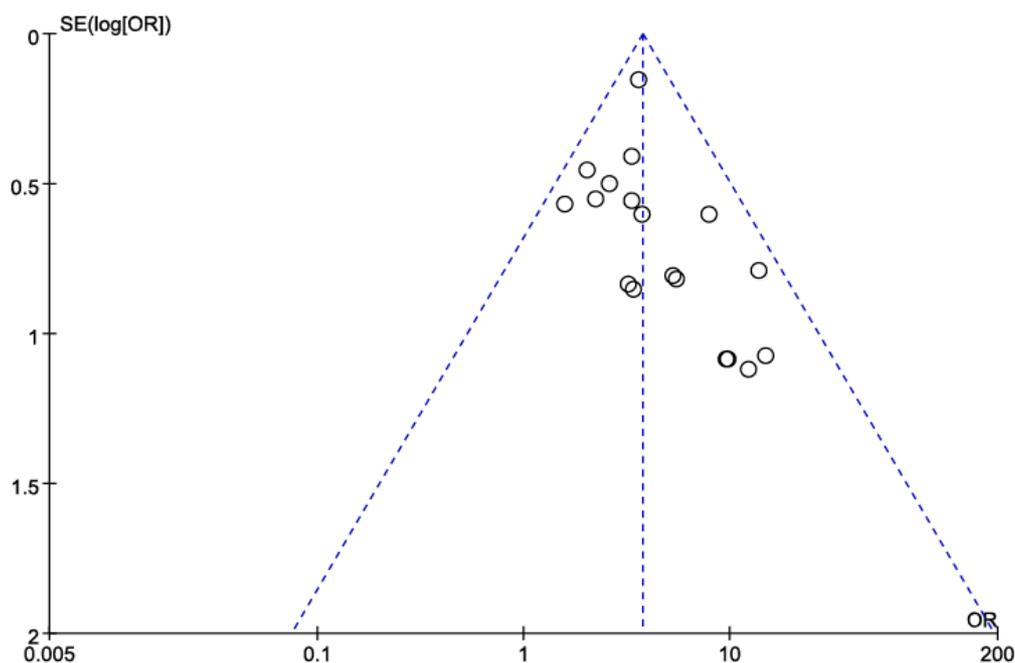


Figure 5: Funnel plot for the total effective rate

DECLARATIONS

Acknowledgement

We thank the authors of the included studies for clarification of the existing data.

Conflict of interest

No conflict of interest is associated with this study.

Authors' contribution

We declare that this work was performed by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xin Jia, Jichun Wang, and Hongai Liu performed the literature search, data analysis, writing and submitting of the manuscript. Dongmei Song, Hongying Duo, and Baoping He assisted in translation, data processing and analysis, literature search, and edited the manuscript.

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