

Shuanghuanglian Injection for Viral Pneumonia: A Protocol for Meta-analysis

YANG YUAN

Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

<https://orcid.org/0000-0001-7624-3963>

Quan Zheng

First People's Hospital of Suining

Mingjun Hu

First People's Hospital of Suining

Zhilin Si

First People's Hospital of Suining

Shuncheng Xie

First People's Hospital of Suining

Zhi Li

First People's Hospital of Suining

Chengshi He (✉ 58133532@qq.com)

Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China.

Protocol

Keywords: viral pneumonia, Shuanghuanglian injection, efficacy and safety, meta-analysis, protocol

Posted Date: January 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-144668/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Viral pneumonia is inflammation (irritation and swelling) of the lungs due to infection with a virus. Rapidly progressing viral pneumonia is associated with considerable mortality, representing a severe threat and imparting a substantial financial burden worldwide. Specific treatments for the viral pneumonia were not yet determined. Recently, Shuanghuanglian injection of Traditional Chinese Medicine was used to treat viral pneumonia. However, there is no systematic reviews have evaluated its efficacy and safety for viral pneumonia.

Methods: We search four English databases (Pubmed, Web of Science, Embase, and the Cochrane library) and four Chinese databases (China National Knowledge Infrastructure, Wanfang Database, Chinese Biomedical Literature Database, Chinese Science and Technology Periodical Database) for all randomized controlled trial of Shuanghuanglian injection for the treatment of viral pneumonia until 11st of December , 2020. Two reviewers individually extracted data from the included randomized controlled trials (RCTs). Data will be synthesized by either the fixed-effects or random-effects model according to a heterogeneity test, Methodological quality assessment and risk of bias will be assessed using the Cochrane bias risk tool. Meta-analysis will be performed using RevMan5.3.5 software provided by the Cochrane Collaboration.

Results: Viral pneumonia has become a disease with substantial mortality. A systematic review assessing the beneficial and harmful effects of Shuanghuanglian injection for viral pneumonia is needed. This study will compare the different outcome indicators of various studies directly and indirectly. This analysis will provide a high-quality synthesis of effectiveness and safety of Shuanghuanglian injection treatment for viral pneumonia. The main outcome indicators include: Outcomes will include mortality, cure rate, efficacy or adverse events confirmed by imaging diagnosis.

Systematic review registration: INPLASY2020120047.

Background

Viral pneumonia is an interstitial pulmonary pneumonia caused by upper respiratory viruses (parainfluenza virus, adenovirus, and respiratory syncytial virus, etc) .The patient may have severe cardiopulmonary dysfunction, which will poses a huge threat to the patient's life[1]. The disease occurs frequently in winter or spring and it can spread out[2]. Recently, the global pandemic of the new type of coronavirus pneumonia (COVID-19) has attracted the attention of the public one again [3]. The virus causes damage to the patients' bronchial epithelial cells, ciliary dyskinesia, and destruction of the phagocytic function of neutrophils, which leads to a decline in respiratory defenses. Patients with viral pneumonia usually have features such as: fever, cough, and rales on auscultation of both lungs[4]. Some severe patients may even have clinical symptoms such as dyspnea, shortness of breath, and chest tightness. Because of the virulence of the pneumonia virus, the age of the patient, and the autoimmune function state are closely related to the occurrence of viral pneumonia, its pathological basis,

pathogenesis, and clinical features are diverse[5]. Due to the genetic mutation of the virus, it is difficult for the human body to form a stable, long-term specific immunity, and the incidence of viral pneumonia is relatively high.

At present, the treatment of viral pneumonia is mainly based on western medicine[6]. The commonly used antiviral drugs in western medicine include amantadine and its analogues, and neuraminidase inhibitors. Amantadine and its analogues have a good therapeutic effect on viral pneumonia caused by influenza A virus, but have no effect on the treatment of viral pneumonia caused by influenza B virus [7], and it can't prevent the infection of influenza A virus[8]. The study found that neuraminidase inhibitors have a good therapeutic effect on influenza A and B viruses: the drug resistance rate of patients is extremely low, the duration of clinical symptoms is short, complications are few, and the length of hospitalization is short too[9]. However, when the human immune system is basically normal, the effective rate of such drugs to prevent influenza is approximately about 70%~93%[10]. Until now, there is still no uniform regulation on whether hormone therapy can be used for viral pneumonia, but it is certain that glucocorticoids are not effective against respiratory syncytial virus [11]. Furthermore, in the treatment of varicella-zoster virus and Hantavirus pneumonia, the use of hormones for anti-inflammatory treatment will aggravate the condition. [12] Clinicians often use high-dose hormone shocks to treat viral pneumonia[13]. During the treatment process, the side effects of hormones are quite obvious. Many patients have increased mortality, severe hypertension, and femoral head necrosis. Because specific antiviral drugs are still lacking, support for symptomatic treatment of viral pneumonia is still the main focus. Study have reported that after immunoglobulin vaccination, it is possible to prevent respiratory syncytial virus infection[14]. Sensitive and specific diagnostic methods and diagnostic methods for viral pneumonia are still to be developed.

Traditional Chinese medicine(TCM) can receive good clinical effects in the prevention and treatment of viral pneumonia[15, 16]. TCM is not only inexpensive, easy to obtain, and has fewer side effects, but also can regulate the patient's own immune function and eliminate or reduce the patient's clinical symptoms. Correcting immune disorders and reducing inflammation is key to the treatment of viral pneumonia. Shuanghuanglian injection is composed of medicinal materials such as honeysuckle, scutellaria baicalensis, and forsythia. It has anti-inflammatory, antiviral, and immune functions. In recent years, Shuanghuanglian injection has become one of the first choice drugs for the treatment of respiratory tract infectious diseases in Chinese medicine hospitals. However, there is no systematic reviews had shown promising its effects and safety for viral pneumonia. The aim of this review is The aim of our study is to objective provide helpful evidence of whether Shuanghuanglian Injection would reduce the mortality and incidence of viral pneumonia. A better understanding of Shuanghuanglian injection can guide the treatment of viral pneumonia.

Methods

We will strictly abide by the requirements of the "Preferred Reporting Items for Systematic Review and Meta-analysis Protocols" to report the meta analysis[17].

Protocol and registration

The protocol registration number was INPLASY2020120047.

Type of study.

Studies were randomized controlled trials (RCTs) using Shuanghuanglian injection for viral pneumonia in adult patients. The language will be limited to Chinese or English. Exclude non-RCT, animal experiments, unclear results indicators such as images, and other nonquantitative indicators. For the articles published repeatedly in Chinese and English journals, the latest one published articles were taken.

Type of Participants.

Participants were adults aged 18 years old and older with the diagnosis of viral pneumonia in the general population, regardless of gender, ethnicity, race, and disease stage. Children, patients with severe cardiovascular diseases and mental illnesses, pregnant women, breast stage, and cancer will be excluded.

Interventions

Interventions included Shuanghuanglian injection alone or in combination with conventional therapy (CT) and/or biological agents for at least 2 weeks. The controls included no treatment, placebo, and CT alone.

Outcome indicators

The main outcome indicators include: the cure rate, mortality, efficacy, or adverse events confirmed by imaging diagnosis. The secondary outcome indicators include: odds ratio, risk ratio, hazard ratios, standardized incidence ratio, standardized mortality ratio, and associated 95% confidence intervals (CIs).

Data sources and search strategies

We will search the following databases will be searched: Pubmed, Embase, Web of Science, the Cochrane library, the China National Knowledge Infrastructure, Wanfang Database, Chinese Biomedical Literature Database, Chinese Science, and Technology Periodical Database. Collect all the RCTs on the treatment of viral pneumonia with Shuanghuanglian injection. And manually search for references in the related literature. The retrieval time is from the inception of the database to December 10, 2020. The language is limited to Chinese and English. The search strategy for PubMed was listed, which was including all search terms. Other searches will be conducted based on these results, and the search strategy will be modified as required for other electronic databases.

#1 search "viral pneumonia" [Title/Abstract]

#2 Search "Shuanghuanglian injection " [Title/Abstract]

#3 Search "RCT" [Title/Abstract] OR "randomized controlled trial" [Title/Abstract]

#4 Search “Efficacy” [Title/Abstract] OR “safety” [Title/Abstract]

#5 #1 and #2 and #3 and #4.

Selection of studies

All initial records from the four electronic databases will be imported into the web-based systematic review Rayyan software[10]. Two authors independently complete the following process: according to the above search strategy to complete the process of document retrieval, import documents into Rayyan software. then, according to the inclusion and exclusion criteria, filter the literature by reading the title and abstract. If it is not possible to determine whether the article meets the requirements based on the inclusion and exclusion criteria, then read full text to select. All the procedures will be carried out by 2 independent reviewers and completed a cross-check. Any conflict will be resolved by discussion with the 3rd author. The process of research selection is shown in Fig. 1.

Data extraction

The data will be extracted out by two independent reviewers in accordance with the Cochrane Handbook of Systematic Reviews of Interventions. Two investigators will independently screen all the included studies to extract the following data: name of the first author, publication year, study design, country, intervention, control group, study period, sample size, numbers of outcomes, age at enrollment, sex, duration of follow-up, adjustments, and effect estimates. The reviewers fill the extracted information into a pre-built Excel table. If necessary, we will contact the trial author for further information.

Dealing with missing data

If there is data loss in the included study, we will contact the original author of the article to obtain the original information. If the missing data is still not available, the existing data will be analyzed and a sensitivity analysis will be performed to address the potential impact of the missing data.

Risk of bias assessment and quality of selected studies

Two researchers independently evaluated the risk of bias in randomized controlled trials in accordance with the Cochrane Handbook of Systematic Reviewers, including the following items: random sequence generation, allocation concealment, blind participants and personnel, blind assessment of results, incomplete result data, selective reports, and other biases. The quality of studies was classified as being at of high, unclear, or low risk of bias. After completion, they would recheck. In the case of a disagreement, they would discuss. If no agreement could be reached, a decision would be made in consultation with researchers from the third party.

Statistical analysis

Statistical analyses were performed using RevMan 5.3 software. Dichotomous data. The relative risk (RR) was calculated with 95% confidence intervals (CI). Continuous data. A fixed-effect mean difference (MD) with 95% CI was calculated for outcomes reported in the same scale, and the

standardized mean difference (SMD) with 95% CI was calculated for outcomes reported in difference scales.

Assessment of heterogeneity: For the meta-analysis of non-significant heterogeneity, we applied a fixed-effect model (FEM), otherwise, Statistical heterogeneity was calculated using the I² statistic, and > 50% was considered to be substantial. Subgroup analyses were performed to explore heterogeneity, and a random-effects model was applied.

Subgroup analysis: When heterogeneity is detected, we will judge the source of heterogeneity through subgroup analysis (e.g., different types of Chinese medicines therapies, research quality, publication age, participation population, and length of treatment). In addition, we can also observe the relationship between the effect values and grouping variables.

Publication bias

The Cochrane Collaboration's Risk of Bias Tool was used to assess bias[18]. Seven domains of risk were assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias(baseline balance and funding/conflict of interest). Publication bias for meta-analysis of ≥ 10 studies was also assessed by using funnel plots and Egger test.

Assess the quality of evidence

The evaluation of the strength of the evidence will be based on the grading of recommendations assessment, development, and evaluation system, there are 4 levels of evidence strength: high, medium, low, or very low.

Discussion

Respiratory tract infections are important components of respiratory diseases that have become one of the major death threats worldwide[19]. Viral pneumonia is a common respiratory disease caused by viral infection. It can easily cause obvious respiratory diseases due to the lung tissue of the affected area and the inflammation changes of the trachea and bronchus, which can affect the normal life and work of patients[20]. TCM has the characteristics of multi-component, multi-target, and multi-channel treatment. It has a long history of treating viral diseases and has remarkable efficacy. Although Shuanghuanglian injection has significant advantages of multiple approaches and multiple targets in the treatment of viral pneumonia. However, due to the complex composition of Chinese medicines, potential safety hazards may exist. Therefore, The purpose of this meta-analysis is to systematically summarize and evaluate the efficacy and safety of Shuanghuanglian injection in the treatment of viral pneumonia. It will help clinicians to timely adopt treatment methods based on the diagnosis results and prevent further expansion of viral pneumonia, which has important clinical significance for the early treatment and rehabilitation of patients.

Abbreviations

95% CI = 95% confidence interval, IF = inconsistency factor, RCT = randomized controlled trial, PRISMA-P = preferred reporting items for systematic review and meta-analysis protocols, TCM = traditional Chinese medicine, CT = conventional therapy, COVID-19=Novel Coronavirus Pneumonia.

Declarations

Acknowledgements

Not applicable

Authors' contributions

CH is the guarantor. CH, YY and QZ contributed to the conception of the study. The manuscript presenting the protocol was drafted by YY and revised by CH. The search strategy was developed by all authors and will be run by QZ and MH, who will also independently screen the potential studies, extract data from included studies and assess the risk of bias. ZS and SX will conduct and finish the data synthesis. QZ and ZL will arbitrate in cases of disagreement and ensure no errors occur during the study. All authors critically revised the draft and approved the final manuscript as submitted.

Funding

This work was supported by the the department of Science and Technology of Sichuan Province, grant number: 2016JY0008.

Availability of data and materials

All data generated or analyzed during this study will be included in the published article and its supplementary files. Should any additional information be required, it will be made available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China. ²First People's Hospital of Suining City ,Suining , Sichuan, China.

References

1. Ciotti M , Maurici M , Santoro V , et al. Viruses of Respiratory Tract: an Observational Retrospective Study on Hospitalized Patients in Rome, Italy[J]. *Microorganisms*, 2020, 8(4):501.
2. Mengjie G , Lingjia Z , Jie S , et al. Analysis on epidemics of priority communicable diseases in China In winter and spring of 2017-2018[J]. *Disease Surveillance*, 2018.
3. Hossain M B . Global Outbreaks of SARS-nCoV-2 (COVID-19 Pandemic) and Spread out in Bangladesh[J]. 2020.
4. Talha M , Ahmed M D , Ullah A , et al. Review on structural mechanism and mode of action of corona virus[J]. *World Journal of Biology and Biotechnology*, 2020, 5(3):35-40.
5. Han M S , Yun K W , Lee H J , et al. Contribution of Co-Detected Respiratory Viruses and Patient Age to the Clinical Manifestations of Mycoplasma Pneumoniae Pneumonia in Children[J]. *The Pediatric Infectious Disease Journal*, 2018:1.
6. Liu X , Cao W , Li T . High-Dose Intravenous Immunoglobulins in the Treatment of Severe Acute Viral Pneumonia: The Known Mechanisms and Clinical Effects[J]. *Frontiers in Immunology*, 2020, 11.
7. Jefferson T , Demicheli V , Rivetti D , et al . Antivirals for influenza in healthy adults . Systematic review [J] . *Lancet* . 2006 ; 367 (9507) : 303 - 313 .
8. Monto AS . The role of antivirals in the control of influenza [J] . *Vaccine* . 2003 ; 21 (16) : 1796 - 1800 .
9. Roberts NA . Treatment of influenza with neuraminidase inhibitors . Virological implications [J] . *Philos Trans R Soc Lond B Biol Sci* . 2001 ; 356 (1416) : 1895 - 1897 .
10. Moscona A . Neuraminidase inhibitors for influenza [J] . *N Engl J Med* . 2005 ; 353 (13) : 1363 - 1373 .
11. Jartti T , Vanto T , Heikkinen T , et al . Systemic glucocorticoids in childhood expiratory wheezing: Relation between age and viral etiology with efficacy [J] . *Pediatric Infectious Disease Journal* . 2002 ; 21 (9) : 873 - 878 .
12. Cheng VC , Tang BS , Wu AK , et al . Medical treatment of viral pneumonia including SARS in immunocompetent adult [J] . *Journal of Infection* . 2004 ; 49 (4) : 262 - 273 .
13. Falagas ME , Vouloumanou EK , Baskouta E , et al . Treatment options for 2009 H1N1 influenza: Evaluation of the published evidence [J] . *International Journal of Antimicrobial Agents* . 2010 ; 35 (5) : 421 - 430 .
14. Simmons C , Farrar J . Insights into inflammation and influenza [J] . *New England Journal of Medicine* . 2008 ; 359 (15) : 1621 - 1623 .
15. Yang F , Zheng W , Zhang J , et al. Whole-process prevention and treatment model of traditional Chinese medicine for coronavirus disease 2019 epidemics [J]. *Zhonghua w zhong bing ji jiu yi xue*, 2020, 32(8):897-899.

16. Wang Q , Wang C , Mei J , et al. Understanding and prevention of D-dimer elevation in coronavirus disease 2019 in traditional Chinese medicine[J]. Zhonghua wei zhong bing ji jiu yi xue, 2020, 32(5):622-624.
17. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
18. HJG S. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons Ltd; 2008.
19. Saito N,Itoga M,Tamaki M,et al. Cough variant asthma patients are more depressed and anxious than classic asthma patients, J. Psychosom. Res. 79 (1) (2015) 18–26.
20. Fontes C A P , Alair Augusto Sarmet Moreira Damas,Dos Santos, Solange Artimos D O , et al. Influenza A virus H1N1 associated pneumonia - acute and late aspects evaluated with high resolution tomography in hospitalized patients[J]. Multidisciplinary respiratory medicine, 2020, 2020,15(1):692.

Figures

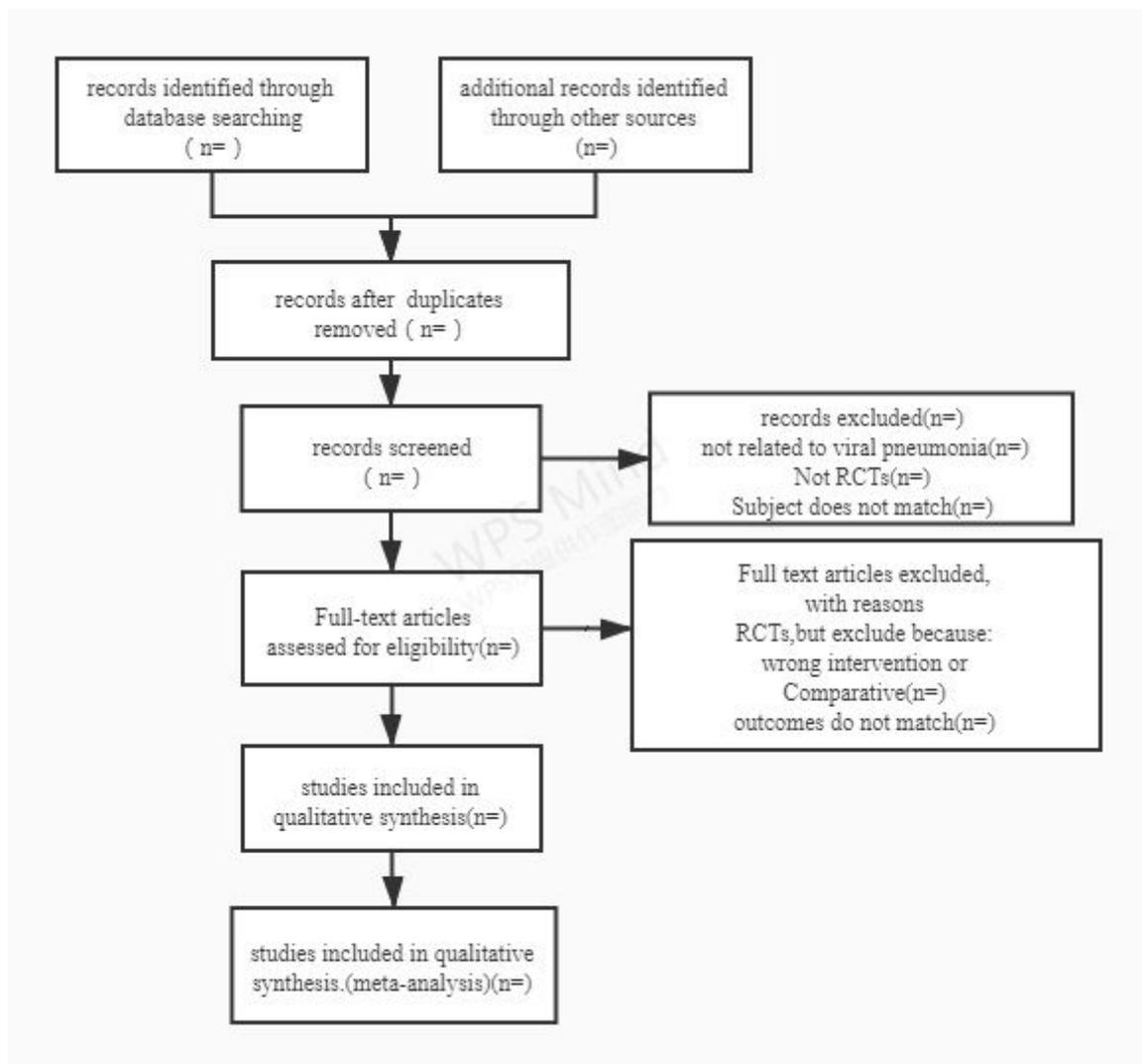


Figure 1

Flow diagram of study selection process.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAP2015checklist.docx](#)