Research Square

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Penehyclidine Hydrochloride Has the Function of Lung Protection for Acute Lung Injury in Rat Models:A Systemic Review and Meta-analysis

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Abstract

Objective

This systematic review and meta-analysis aims to review the effects of penehyclidine hydrochloride (PHC) on acute lung injury in animal models.

Methods

PubMed, Embase, CNKI were searched for collecting the randomized controlled trials(RCTs) on the effects of penehyclidine hydrochloride on acute lung injury in rat models from inception to July 1, 2021. We used Cochrane evaluating quality and RevMan 5.3 software performing Meta-analysis.(lung W/D ratio、PaO2/FiO2、SOD、MPO activity、IL-6 and TNF-α)

Results

Our search including 11 studies in 3 databases. Meta-analysis showed that, Compared with the acute lung injury model group, the PHC treatment group: lung W/D ratio[MD=-1.29，95%CI：-1.94，-0.64，P＜0.01]、PaO2/FiO2[MD=1.73，95%CI：0.01，3.45，P＜0.01]、SOD[MD=7.05，95%CI：5.58，8.52，P＜0.000,01]、IL-6 [MD=-1.03，95%CI：-1.29，-0.77，P＜0.0001]、IL-6 [MD=-3.35，95%CI：-5.29，-1.40，P＜0.001]and TNF-α[MD=-2.17，95%CI：-3.27，-1.07，P＜0.0001].

Conclusions

penehyclidine hydrochloride has the function of lung protection in acute lung injury and provides a new therapy for future clinical treatment.

Introduction

Acute lung injury (ALI) is a continuum of lung changes caused by infection, collagen vascular diseases and shock. It is typically characterized by inflammatory changes, dyspnea, and refractory hypoxemia that typically presents finally as respiratory distress syndrome(ARDS), resulting in raised morbidity [1].

Studies have found that the inflammatory mechanism is very important for ALI's occurrence and development[2-4]. Shock, oxidative stress and other factors can stimulate the production of upstream Toll-like receptor 4 (TLR4) factor, which can effectively start the inflammatory signal pathway[5]. After the activation of the NF-κB signal pathway, it can further induce the activation of downstream inflammatory cells, to produce the inflammatory cascade effect, so that the inflammatory process can be amplified and sustained. Finally, it acts on the lung tissue, leading to inflammatory injury[6, 7]. Recent studies have found that the PHC has the function of lung protection and inflammation inhibitation[8, 9] . Therefore, PHC is an alternative drug for the treatment of acute lung injury. However, its efficacy and mechanism have not been systematically evaluated and analyzed. Therefore, we evaluated the effect of PHC intervention

through the Meta-analysis, in order to understand the therapeutic effect of PHC for acute lung injury in rat models.

Methods

Study inclusion and Exclusion criteria

inclusion criteria included1) Randomized Controlled Trial (RCT);2) animal studies; Languages: Chinese and English; 3) Languages: Chinese and English; 4) Intervention measures: The experimental group was penehyclidine hydrochloride treatment group, and the control group was the same amount of normal saline injection or other treatments alone.

Exclusion criteria included 1)incomplete experimental data and unclear experimental methods; studies published as review, case report or abstract; 2) Clinical trial research, reviews, case reports or retrospective analysis; 3) duplicate publications.

Study quality assessment

The Camaradesi list score was used independently by two authors(Shasha LUO and Dongwei Wang)to evaluate the methodological quality of trials. We discuss and resolve when there is a disagreement. The Camaradesi list scoring system(ranging from 1 to 10)includes; 1)Sample size calculation□2□ Randomization process; 3□Blindedness model induction of acute lung injury; 4□Blindedness assessment; 5) Appropriate mouse model; 6)Application the anesthetics do not significantly improve the degree of lung injury; 7)Control the temperature; 8)Published after peer review; 9)Comply with the animal protection law; 10□Declarate potential conflicts and interest.YES scores 1 point, NO does not score. Higher scores indicate exceptional methodologic qualities, and lower scores suggest poor qualities.

Data abstraction

Two authors extracted independently the included studies (research general information ,intervention and control measures, observation indicators and research results)and then checked them. The authors of the included studies were contacted if the information is not comprehensive .

Statistical analysis

All data were provided by utilizing RevMan (version 5.3, Cochrane, α=0.05.), and all including studies were tested for heterogeneity □χ^2 test□, the fixed-effects model is used for Meta-analysis when the homogeneity is good (P>0.10, I^2<50%); conversely,the random-effects model is used when the heterogeneity is statistically significant (P<0.10, $I^2 \geq 50\%$).

Results

Included studies search

We searched 135 articles in 3 databases. Finally, 11 articles were included in the meta-analysis by reading the abstract and the main text.Document retrieval processes were presented in Figure 1.

Characteristics of included studies

1.Acute lung injury model

Most of the models are induced by injecting LPS or blunt chest trauma. Among the anaesthesia，they used Chloral Hydrate（ip），pentobarbital（iv）and ketamine/xylazine (iv).

2.PHC intervene

PHC dosages ranged from 0.3 mg/kg to 5 mg/kg. PHC was administered 30 - 60 min before model establishment .（As shown in Table 1)

Table 1. data of the included studies (n = 11)

Study	Acute lung injury model	Anaesthesia	PHC group		Contol group	Outcomes
			Dose	Timing		
Jia Zhan，2011	cecal ligation	hloral Hydrate (ip)	0.3mg/kg	before ALI 1 h	Saline	①、④、⑤
			0.4mg/kg	before ALI 1 h	Saline	
RongtaoZhu，2018	acute pancreatitis	chloral hydrate (im)	0.2 mg/kg	30 min prior to ALI	Blank sodium chloride	③、④、⑤
Xiaojing Wu，2019	intratracheal administra-	pentobarbital (iv)	0.5 ml(2 mg/kg)	30 min prior to ALI	Saline Saline	③、④、⑤
Zhaohui Liu，2020	induced renal ischemia	NR	1mg/kg	30 min after ALI	Blank	②、③
Shaobing Ye，2020	LPS	NR	0.5 mg/kg 1 mg/kg	prior to ALI	PBS	②、③
			2.5 mg/kg		PBS	
Junting Weng，2019	LPS	pentobarbital (iv)	1mg/kg	1h	LPS	②、③、④、⑤
			2.5mg/kg	1h		
			5mg/kg	1h	Blank	
Hao Li，2011	cecal ligation	ketamine(iv)	0.45mg/kg	1 h after ALI	saline saline Blank	②、③
Na Wang，2012	LPS	pentobarbital (iv)	0.3mg/kg	1 min following ALI	saline	④、⑤
			1 mg/kg	1 min following ALI		
			3mg/kg	1 min following ALI	saline containing LPS	
Weifeng Shen，2009	LPS	pentobarbital （iv）	0.3mg/kg	30 min prior to ALI	saline	①、②、③
			1mg/kg	30 min prior to ALI	methylprednisolone	
			3mg/kg	30 min prior to ALI	saline	
Qian Kong，2019	blunt chest trauma	pentobarbital (iv)	2 mg/kg	30 min prior to ALI	saline	①
			2 mg/kg	60 min prior to ALI	saline	
Xiaopeng Wang，2020	LPS	NR	0.3mg/kg	30 min before ALI	LPS	④、⑤
			1mg/kg	30 min before ALI		
			3mg/kg	30 min before ALI	saline	

（PaO2/FiO2），SOD），lung W/D ratio），IL-6），TNF-α.

Quality Evaluation

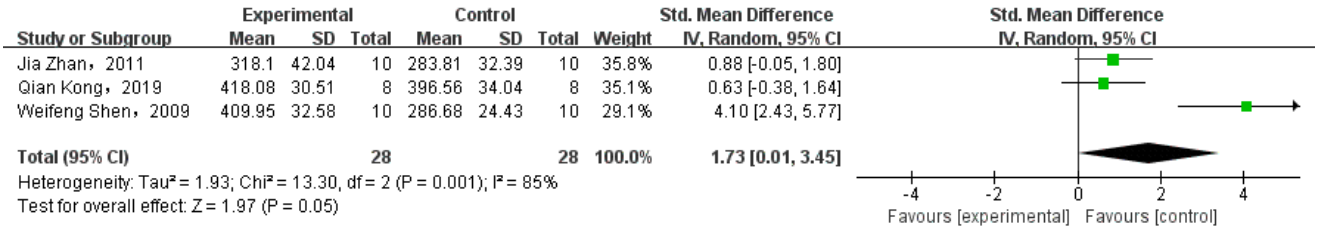
1)Sample size calculation，2）Randomization process; 3）Blindedness model induction of acute lung injury; 4）Blindedness assessment; 5) Appropriate mouse model; 6)Application the anesthetics do not significantly improve the degree of lung injury; 7)Control the temperature; 8)Published after peer review; 9)Comply with the animal protection law; 10）Declarate potential conflicts and interest.YES scores 1 point, NO does not score. Higher scores indicate exceptional methodologic qualities, and lower scores suggest poor qualities.

Table 2.The Quality Evaluation of Eligible Studies (n = 11)

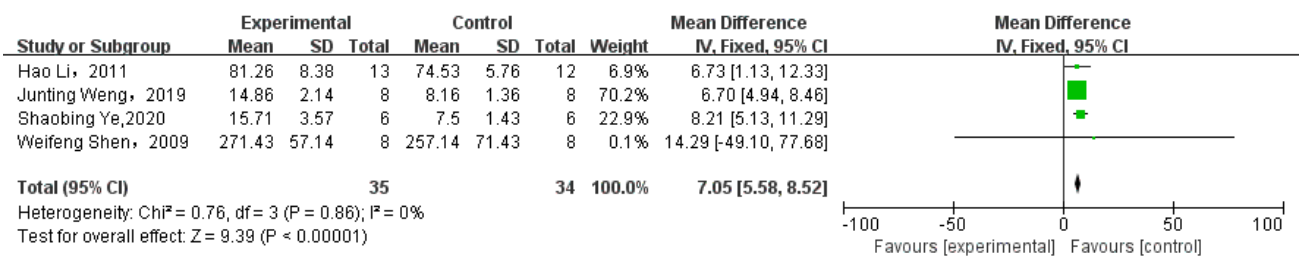
Study		1	2	3	4	5	6	7	8	9	10	Score
Jia Zhan	2011		√	√		√	√		√	√		6
Rongtao Zhu	2018	√	√	√		√	√		√	√	√	8
Xiaojing Wu	2019	√				√	√		√			4
Zhaohui Liu	2020		√	√		√	√	√	√	√	√	8
Shaobing Ye	2020	√	√	√		√	√	√	√	√	√	9
Junting Weng	2019	√	√	√		√	√	√	√	√	√	9
Hao Li	2011	√	√	√		√	√	√	√	√	√	9
Na Wang	2012	√	√	√		√	√	√	√	√		8
Weifeng Shen	2009	√	√	√		√	√		√	√		7
Qian Kong	2019	√	√	√		√	√	√	√	√	√	9
Xiaopeng Wang	2020	√	√	√		√	√	√	√	√	√	9

Meta analysis's result

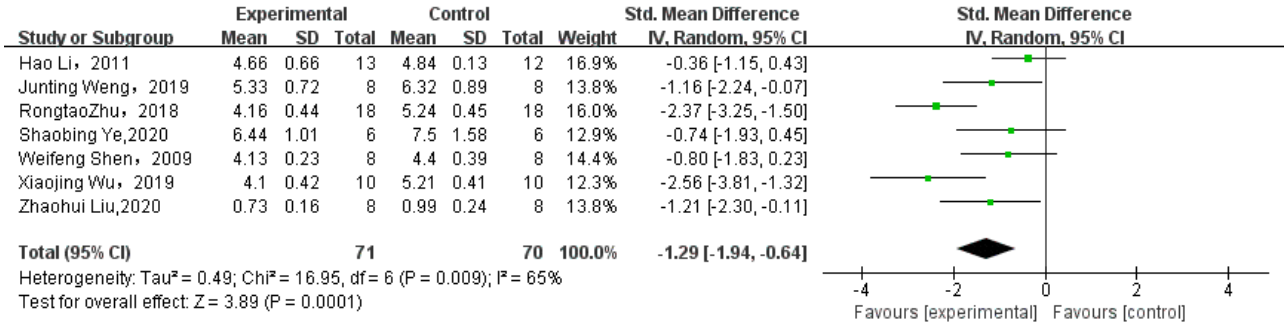
A.PaO2/FiO2，B.SOD，C.lung W/D ratio，D.IL-6，E.TNF-α.



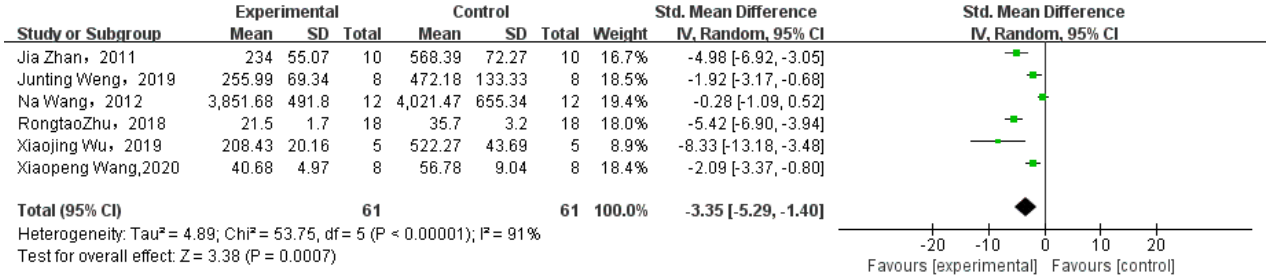
A



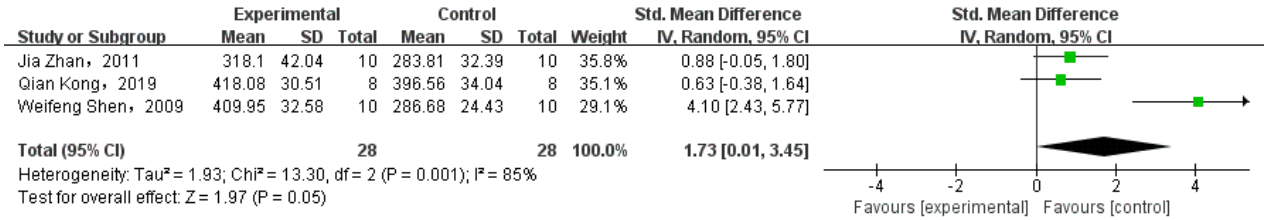
B



C



D



E

1.PaO2/FiO2

This included 3 articles[10-12] to evaluate lung function through applying Oxygenation Index. There was statistical heterogeneity between the results of each study (I^2=93%, P<0.0001), so we used the random-effects model. Compared with the control group, PHC affected on improving the oxygenation index of the lungs[RR=1.73, 95%CI (0.01, 3.45), P<0.01]. (Figure A)

2.SOD

This included 3 articles[12-15] detected SOD in lung tissues. There was statistical heterogeneity between the results of each study (I^2=80%,P<0.01).we excluded the articles(Zhaohui Liu, 2020) after sensitivity analysis, the heterogeneity disappears. Compared with the control group, PHC affected on improving the SOD.[RR=7.05, 95%CI (5.58, 8.52), P□0.00001] (Figure B)

3.lung W/D ratio

This included 7 articles[12-18].Due to the different measurement units among the studies, we used the random-effects model.The lung wet-to-dry ratio of the PHC group is lower than the control group. [MD=-1.29,95%CI(-1.94, -0.64), P<0.001](Figure C)

4.IL-6 and TNF-α

This included 6 articles[13-15, 17, 19, 20].Due to the different measurement units among the studies, we used random effects model. The IL-6 and level of the PHC group is lower than the control group.[IL-6:MD=-3.35,95%CI(-5.29, -1.40), P<0.0001; TNF-α:MD=-2.17,95%CI(-3.27, -1.07), P<0.01](Figure D□E)

Discussion

ALI is one of the most common clinical illnesses. With the development of the disease, it will threaten the life of patients and economic of society[21]. Therefore, it is very important for us to find a suitable treatment for ALI. Studies have shown that ALI is closely related to inflammation[2-4]. That is the reason why PHC is a good choice for the treatment of ALI, which can reduce inflammation and protect the lung [8, 9]. At present, the application of PHC in animal models of acute lung injury has become more popular. Our study aims to clarify the effect of PHC for acute lung injury in rat models and provides a new treatment.

This study reviews systematically the studies of acute lung injury in rat models treatment with PHC .Based on the current evidence, PHC treatment can significantly reduce the IL-6, TNF-α, and lung W/D ratio, it can also increase SOD and lung oxygenation index.So it has a good effect on the lungs. Although the results show that PHC is beneficial, the heterogeneity is not satisfactory. The analysis may have the following reasons: 1. the quality of the included studies are not high; 2. the dose and time of PHC are different; 3. the rat species establish are different.

Limitations of systematic reviews

Although meta-analysis shows that PHC has certain advantages in acute lung injury treatment, the meta-analysis cannot replace multi-center RTC. In addition, we found that there are large differences in the mouse model ling methods, PHC doses, and PHC inject time. That is why the heterogeneity is not satisfaction. Therefore, we need more evidence support of double-blind RCT, and then select unified experimental standards. Only in this way our research results can be more reliable.

Declarations

Authors' contributions

Shasha Luo analyzed the data and wrote the paper. Hongbao Tan□Li Chen□Dongwei Wang and Rong Hua revised and edited the paper.

All authors read and approved the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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Conflict of interest

The author declares that she has no conflict of interest.

Availability of data and materials

Not available.

Ethics approval and consent to participate

Not available.

Acknowledgements

Not available.

Consent for publication

The author consents to the publication of the manuscript in European Journal of Medical Research.

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Figures

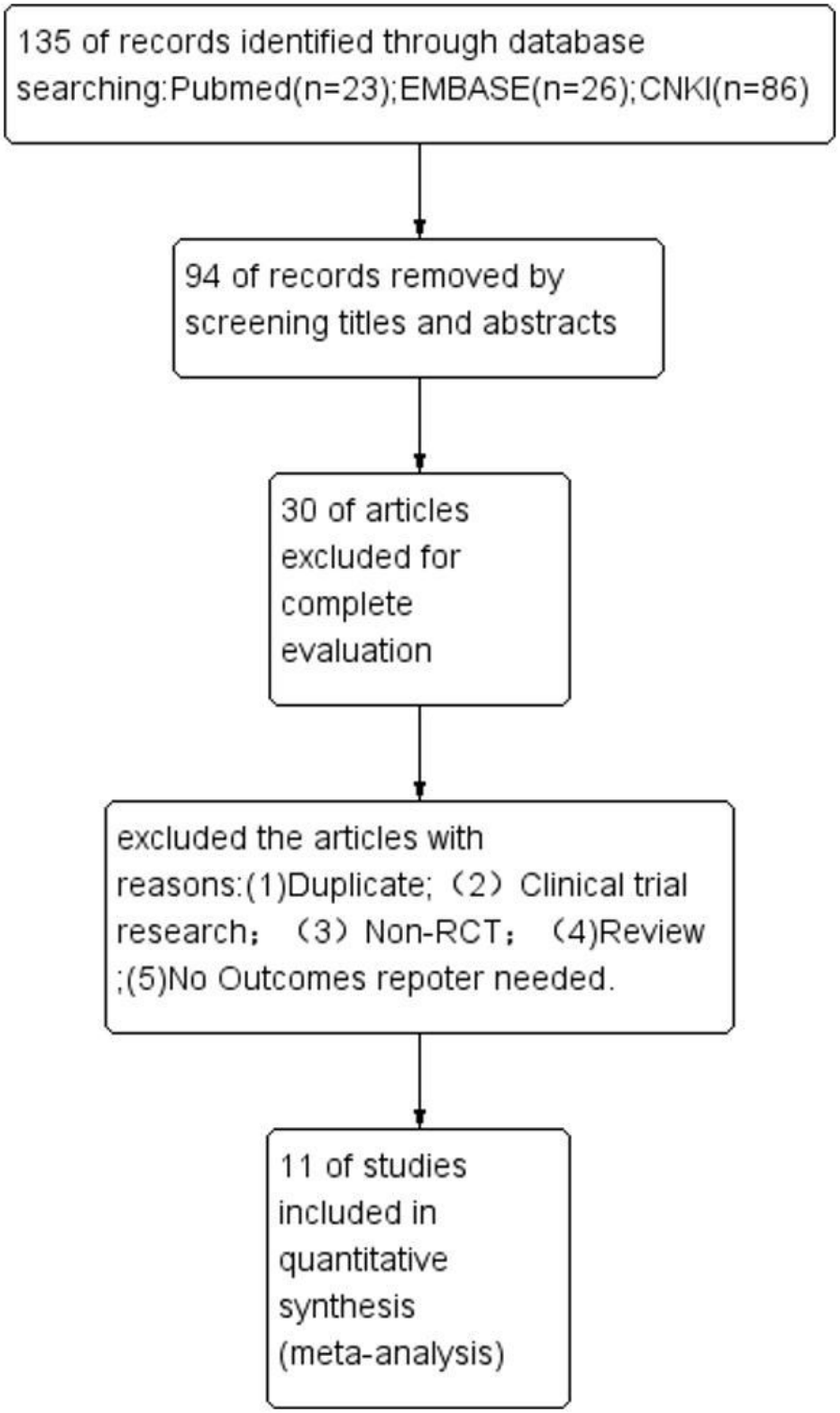

Figure 1

Flow chart of literature selection.