INPLASY PROTOCOL

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None declared.

Comparative Efficacy and Safety of Non-Medical Therapy for Pulmonary Hypertension: A Systematic Review and Network Meta-Analysis

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Review question / Objective: This meta-analysis aims to estimate the effectiveness of different non-medical therapy on patients with pulmonary hypertension in single or double-blinded randomized controlled trials.

Condition being studied: Pulmonary hypertension (PH) (defines as a mean pulmonary artery pressure ≥ 25 mmHg at rest on right-heart catheterization) comprises a complex group of conditions, characterized by increased right ventricular after load, which ultimately leads to right heart failure.

Information sources: Relevant articles are searched and selected from published data in electronic databases PubMed, Cochrane Library, MEDLINE, Embase, CNKI, Wanfang and VIP database (from inception until October 1, 2021)with the restriction on language: English and Chinese.

INTRODUCTION

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METHODS

Participant or population: Adults with PH (men and women; age 18 years), independent of whether the subjects are stable on therapy (change of treatment over the past 3 months) are included in this study.

Intervention: Interventions in the non-medical therapy group include aerobic training, resistance training, anaerobic training, supervised aerobic training, unsupervised aerobic training, supervised resistance training, etc.

Comparator: Interventions for the control group include exercise methods, such as aerobic, interval, strength, combined training (aerobic and strength), respiratory training, or no exercise training.

Study designs to be included: RCT.

Eligibility criteria: Studies will be included if they conform to the following criteria: (1)randomized controlled trial (RCT) as study design;(2)Adults with PH (men and women; age 18 years), independent of whether the subjects are stable on therapy (i.e., change of treatment over the past months) are included in this study. (3) RCTs of non-medical therapy in PH patients are included. In this study, non-medical therapy includes aerobic training, resistance training, anaerobic training, supervised aerobic training, unsupervised aerobic training, supervised resistance training, unsupervised resistance training, combined aerobic training and resistance training, flexibility training, no exercise and other physical therapy. The exclusion criteria are: (1) non-RCTs, studies with insufficient data, duplicated publications, conference reports, systematic reviews, or different studies from the same sample origin; (2) participants restricted neonatal patients or pediatric; (3) crossover,2x2 factorial, retrospective studies.

Information sources: Relevant articles are searched and selected from published data in electronic databases PubMed, Cochrane Library, MEDLINE, Embase, CNKI, Wanfang and VIP database (from inception until August 1, 2022, with the restriction language: English and Chinese.

Main outcome(s): 1. Six-minute walk distance (6MWD). 2. Peak oxygen uptake (VO2peak). 3. Peak power output (Wpeak).

Quality assessment / Risk of bias analysis: Two review authors independently assess the included studies for risks of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We assess the following domains: 1.Random sequence generation. 2.Allocation concealment. 3.Blinding of participants and personnel. 4.Blinding of outcome assessment. 5.Incomplete outcome data. 6.Selective outcome reporting. 7.Other potential sources of bias.

Strategy of data synthesis: The network meta-analysis is performed using Stata (version 16.0, Stata SE), Review Manager (version 5.3, The Nordic Cochrane Centre, Copenhagen, Den-mark), and R software (version 4.0.3, R foundation for statistical computing). The odds ratio (OR) with corresponding 95% confidence interval (CI) and mean difference(MD) with corresponding 95% confidence interval (CI) are utilized to compare different exercises with respect to various clinical outcomes. Indirect comparisons are performed based on the Bayesian framework model using the "gemtc" package of the R 3.5.3 software. OS is estimated using the hazard ratio (HR) with 95% confidence interval (CI). A 2-tailed $p < 0.05$ is considered statistically significant. Based on the deviance information criterion (DIC) value, a fixed, or random-effects model is applied to the Bayesian framework model for data analysis. The convergence of the models is assessed with Brooks-Gelman-Rubin, trace, and density plots. A funnel plot is used to assess publication bias. Rank probabilities are calculated to determine the hierarchy of treatments. The "mtc.anohe" command in the "gemtc"

package is used to evaluate global heterogeneity, which is documented with the variance parameter I2; a value >50% is considered indicative of significant heterogeneity. The geometry of the treatment network is established using the R software. Inconsistency is assessed if any closed loop existed in the network. The stability of the results is obtained by sensitivity analyses with discarding each study sequentially. we use surface under the cumulative ranking (SUCRA) probability, which presents as a percentage the efficacy or safety of every intervention that is always best without uncertainty. The Node-splitting approach was used to assess the inconsistency.

Subgroup analysis: About half of the causes of PAH in the Western population are IPAH, HPAH, and drug-associated PAH, and connective tissue diseases which systemic sclerosis accounts for about 2/3 of are the most common cause in APAH. And the causes of PAH in the Asian population are significantly different from the Western population. In the Asian population, Congenital heart disease is the most common cause of PAH, followed by IPAH and PAH associated with connective tissue disease in which systemic lupus erythematosus and Sjogren's syndrome are the most common cause. Therefore, in order to avoid the difference of treatment outcomes because of populations from different districts, patients were divided into groups depending on Asian or non-Asian populations to verify the internal consistency of the results of the clinical trial or explore the optimal benefit population.

Sensitivity analysis: Stratified meta-analysis is performed on the included literature according to the size of the sample size to investigate whether the conclusions have changed.

Country(ies) involved: China.

Keywords: Non-Medical Therapy; Pulmonary hypertension; Quality of life; Exercise capacity; Randomized controlled trial.

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