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Different functions for extracellular vesicles from different mesenchymal stem cells in Bone regeneration: A systematic review with meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 March 2025 and was last updated on 24 March 2025.

INTRODUCTION

Review question / Objective What is the effect of inhaled corticosteroids on long-term health outcomes in adults with chronic obstructive pulmonary disease?

Condition being studied Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterized by persistent airflow limitation and inflammation of the airways. It is primarily caused by long-term exposure to harmful particles or gases, such as cigarette smoke, and is associated with symptoms like coughing, sputum production, and shortness of breath. COPD significantly impacts quality of life and is a leading cause of morbidity and mortality worldwide. Despite current treatment options, there is no cure for COPD, and patients often require long-term management strategies to control symptoms and reduce disease progression.

METHODS

Participant or population The types of participants addressed in this review will include adults aged 18 years and older diagnosed with chronic obstructive pulmonary disease (COPD) according to established guidelines, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria or other validated diagnostic standards. Participants will be recruited from studies that focus on patients with stable COPD or those experiencing acute exacerbations of COPD. Exclusions may include individuals with comorbidities unrelated to COPD or those who have contraindications to inhaled corticosteroid therapy, depending on the specific study criteria.

Intervention The interventions to be evaluated in this review will focus on the use of inhaled corticosteroids (ICS) as a treatment for chronic obstructive pulmonary disease (COPD). This includes evaluating ICS monotherapy and

combinations with long-acting beta-agonists (LABA), such as fluticasone furoate/vilanterol or budesonide/formoterol. The review will compare these interventions to other therapies, such as inhaled bronchodilators alone or placebo, to assess their efficacy and safety profiles in managing COPD symptoms, reducing exacerbations, and improving lung function.

Comparator Placebo or standard care without EVs therapy.

Study designs to be included The study designs to be included are randomized controlled trials (RCTs) and observational studies (cohort studies, case-control studies). These designs will address the objective of comparing the long-term health effects of inhaled corticosteroids versus other interventions or placebos in patients with chronic obstructive pulmonary disease.

Eligibility criteria
Inclusion criteria:
Published in English between 2015 and January 2023.
In vivo randomized controlled trials (RCTs) using preclinical animal models of bone defects (rats, mice, rabbits).
Exclusion criteria:

Studies not reporting primary or secondary outcomes (BV/TV, histological score, biomechanical properties).
Non-randomized designs, in vitro studies, or clinical trials involving human subjects.

Information sources PubMed, Embase, and Web of Science (searched from January 2015 to January2023).

Main outcome(s) Bone Volume Fraction (BV/TV): This will be the primary outcome to assess the therapeutic effect of MSC-EVs on bone regeneration. BV/TV measures the proportion of bone volume relative to total tissue volume and is a critical indicator of bone healing and remodeling.

Additional outcome(s) Histological Scores: These scores evaluate the quality of newly formed bone, including parameters such as osteoid formation, mineralization, and integration with surrounding tissues.
Biomechanical Parameters: These include measures of mechanical strength, such as compressive or torsional strength, to assess the functional recovery of bone following MSC-EV treatment.

Quality assessment / Risk of bias analysis
Assessment of Risk of Bias: The risk of bias for each included RCT will be assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Each trial will be categorized as having a “low,” “high,” or “unclear” risk of bias in key domains.
Data Synthesis Methods:
For continuous outcomes (e.g., BV/TV improvement), weighted mean differences (WMD) with 95% confidence intervals (CI) will be calculated to compare the intervention and control groups.
For binary outcomes, risk ratios (RR) or odds ratios (OR) with 95% CI will be used as appropriate.
Meta-Analysis Tools: RevMan software will be used for data analysis, including effect size calculations, forest plot generation, and assessment of heterogeneity using the I^2 statistic. A random-effects model will primarily be used to account for potential heterogeneity among studies unless a low level of heterogeneity ($I^2 < 50\%$) is observed.
Sensitivity Analysis: Sensitivity analyses will be conducted to assess the robustness of the results by excluding studies with high risk of bias or exploring the impact of different methodological approaches.
Subgroup Analyses: Subgroup analyses may be performed based on factors such as study design, participant characteristics, and intervention type to explore potential sources of heterogeneity.The methodological quality and risk of bias in the included studies were assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Each randomized controlled trial (RCT) was evaluated for potential sources of bias across key domains, including:
Random sequence generation: Whether the allocation sequence was adequately generated to prevent selection bias.
Allocation concealment: Whether measures were taken to ensure that participants and investigators could not foresee or influence assignment to study groups.
Blinding of participants and personnel: Whether blinding was used to prevent performance bias during interventions.
Blinding of outcome assessment: Whether outcomes were assessed without knowledge of the assigned intervention group to minimize detection bias.
Incomplete outcome data: Whether there was a risk of attrition bias due to missing outcome data for participants.
Selective reporting: Whether outcomes were selectively reported, potentially introducing reporting bias.

For each domain, studies were categorized into "low risk," "high risk," or "unclear risk" of bias based on the available information. The overall risk of bias was visually summarized using a Risk of Bias graph (Figure 2) and Risk of Bias summary table (Figure 3), which provide detailed descriptions.

Strategy of data synthesis The data synthesis strategy will involve the following steps:

Study Selection: Only randomized controlled trials (RCTs) that meet the predefined inclusion criteria will be included in the meta-analysis.

Data Extraction: Extracted data will include study characteristics, sample size, intervention details, control group information, and outcomes of interest (e.g., BV/TV improvement).

Assessment of Risk of Bias: The risk of bias for each included RCT will be assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Each trial will be categorized as having a "low," "high," or "unclear" risk of bias in key domains.

Data Synthesis Methods:

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Sensitivity Analysis: Sensitivity analyses will be conducted to assess the robustness of the results by excluding studies with high risk of bias or exploring the impact of different methodological approaches.

Subgroup Analyses: Subgroup analyses may be performed based on factors such as study design, participant characteristics, and intervention type to explore potential sources of heterogeneity.

This strategy ensures a comprehensive and systematic approach to synthesizing the data from included studies while accounting for methodological quality and potential biases.

Study Selection: Only randomized controlled trials (RCTs) that meet the predefined inclusion criteria will be included in the meta-analysis.

Data Extraction: Extracted data will include study characteristics, sample size, intervention details, control group information, and outcomes of interest (e.g., BV/TV improvement).

Assessment of Risk of Bias: The risk of bias for each included RCT will be assessed using the Cochrane Handbook for Systematic Reviews of Interventions. Each trial will be categorized as having a "low," "high," or "unclear" risk of bias in key domains.

Data Synthesis Methods:

For continuous outcomes (e.g., BV/TV improvement), weighted mean differences (WMD) with 95% confidence intervals (CI) will be calculated to compare the intervention and control groups.
For binary outcomes, risk ratios (RR) or odds ratios (OR) with 95% CI will be used as appropriate.
Meta-Analysis Tools: RevMan software will be used for data analysis, including effect size calculations, forest plot generation, and assessment of heterogeneity using the I^2 statistic. A random-effects model will primarily be used to account for potential heterogeneity among studies unless a low level of heterogeneity ($I^2 < 50\%$) is observed.

Sensitivity Analysis: Sensitivity analyses will be conducted to assess the robustness of the results by excluding studies with high risk of bias or exploring the impact of different methodological approaches.

Subgroup Analyses: Subgroup analyses may be performed based on factors such as study design, participant characteristics, and intervention type to explore potential sources.

Subgroup analysis In the article, subgroup analyses were conducted to explore potential sources of heterogeneity and to assess the impact of specific factors on the outcomes. Subgroup analyses included variables such as species (e.g., rodents vs. dogs), EV source (e.g., BMSC-derived vs. UC-MSC-derived extracellular vesicles), and experimental conditions (e.g., treatment duration or dosage). These subgroup analyses aimed to provide a more detailed understanding of how these factors might influence the effectiveness of

EVs therapy in improving bone volume fraction (BV/TV) compared with controls.

Sensitivity analysis N/A.

Country(ies) involved China.

Keywords Meta-analysis, bone regeneration, mesenchymal stem cells, extracellular vesicles.

Contributions of each author

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