INPLASY PROTOCOL

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The authors declare that they have no competing interests.

Amikacin nebulization for the adjunctive therapy of gram-negative pneumonia in mechanically ventilated patients: A systematic review and meta-analysis of randomised

Qin, JP[1]; Zhou, H[2]; Zhu, Y[3]; Xu, Y[4]; Du, B[5]; Huang, HB[6].

Review question / Objective: **The aim of the present meta-analysis was to review the available published RCTs to investigate the efficacy and safety of nebulized amikacin as an adjunctive therapy in the treatment of critically ill ventilated patients with Gram-negative pneumonia.**
Condition being studied: **Our team members come from a tertiary hospital in China. The team members are familiar with antibiotic atomization treatment. Furthermore, the team members have published several meta-analyses and can successfully complete this study.**
Information sources: **We will search the references in the included trials and personal files. We will request advice from experts in the field. In addition, we will search associated articles from critical care meetings; and contacted the authors of included trials, if need.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2020 and was last updated on 12 July 2020 (registration number INPLASY202070045).

INTRODUCTION

Review question / Objective: **The aim of the present meta-analysis was to review the available published RCTs to investigate the efficacy and safety of nebulized amikacin as an adjunctive therapy in the treatment of critically ill ventilated patients with Gram-negative pneumonia.**

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China. The team members are familiar with antibiotic atomization treatment. Furthermore, the team members have published several meta-analyses and can successfully complete this study.

METHODS

Participant or population: Adult (>18 years old) critically ill ventilated patients with confirmed Gram-negative pneumonia.

Intervention: Patients received nebulized amikacin.

Comparator: Patients received not nebulization or nebulized placebo.

Study designs to be included: We will include only randomised controlled trials in the current study.

Eligibility criteria: RCTs will be included if they report data on any of the predefined outcomes in ventilated adult patients with Gram-negative pneumonia and managed with nebulized amikacin as adjunctive therapy.

Information sources: We will search the references in the included trials and personal files. We will request advice from experts in the field. In addition, we will search associated articles from critical care meetings; and contacted the authors of included trials, if need.

Main outcome(s): The primary outcome is clinical response. Secondary outcomes included overall mortality, pneumonia associated mortality, microbiologic eradication, change of CPIS from baseline after treatment (ΔCPIS), length of stay in ICU, duration of MV and adverse events of bronchospasm and nephrotoxicity. Discrepancies were identified and resolved through discussion.

Quality assessment / Risk of bias analysis: The two investigators independently will assess the quality of RCTs using the risk of bias tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions. The quality of evidence resulting from the present meta-analysis will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Strategy of data synthesis: The results from studies are combined to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) for dichotomous outcomes. As to the continuous outcomes, mean differences (MD) and 95% CI are estimated as the effect results. A p value of less than 0.10 or an I2 value of greater than 50% as indicative was considered of substantial heterogeneity. A random-effects model or a fixed-effects mode (DerSimonian-Laird) will be chosen when significant heterogeneity or non-significant heterogeneity is not observed, respectively.

Subgroup analysis: Subgroup analyses will be performed with regard to primary outcome by pooling studies with the following: 1) types of nebulizers; 2) dose of nebulized amikacin; 3) proportion of patients with drug-resistant bacteria (100% or ≥50% or <50%) and 4) study design.

Sensibility analysis: We will perform sensitivity analyses by omitting one study in each turn to investigate the influence of a single study on the overall pooled estimate of each predefined outcome.

Language: No language limitation was imposed.

Country(ies) involved: China.

Keywords: nebulized amikacin; Gram-negative pathogens; mechanical ventilation; pneumonia; meta-analysis.

Contributions of each author:
Author 1 - Jun-Ping Qin - Dr. Qin will responsible for the data collection, analysis and drafting of the article.
Author 2 - Hua Zhou - Dr. Zhu will do the data collection and analysis.
Author 3 - Yuan Zhu - Dr. Zhou will do the data collection and analysis.

Author 4 - Yuan Xu - Dr Xu will be responsible for the study design and revisions of this manuscript.
Author 5 - Bin Du - Dr Du will be responsible for the study design and revisions of this manuscript.
Author 6 - Hui-Bin Huang - Dr. Huang was responsible for the conception of the study and the integrity of the work as a whole, from inception to publication of the article.