COVER PAGE

Official Title:

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

ClinicalTrials.gov Identifier:

NCT Number: Not yet assigned

Document Type:

Study Protocol

IRB Approval Reference:

IRB PGMI Ref No. 100/24

Date:

03 January 2024

Sponsor:

Lahore General Hospital / PGMI, Lahore, Pakistan

STUDY PROTOCOL

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

1. Background and Scientific Rationale

Ventilator-associated pneumonia (VAP) is a major cause of morbidity and mortality among critically ill patients, particularly in settings with a high prevalence of multidrug-resistant gram-negative organisms. Inhaled antibiotic therapy allows targeted drug delivery to the lungs, achieving high local concentrations while minimizing systemic toxicity. Amikacin, a broad-spectrum aminoglycoside, is well suited for nebulized administration. This study evaluates clinical outcomes of inhaled amikacin as adjunctive therapy in VAP.

2. Study Objectives

Primary Objective: To evaluate clinical improvement in patients with ventilator-associated pneumonia receiving adjunctive inhaled amikacin.

Secondary Objectives: To compare duration of mechanical ventilation, ICU length of stay, and safety outcomes between treatment groups.

3. Study Design

Prospective, randomized, comparative interventional study conducted in the Surgical Intensive Care Units of Lahore General Hospital from 01 January 2024 to 31 December 2024.

4. Study Setting

Two Surgical Intensive Care Units, Lahore General Hospital, Lahore, Pakistan.

5. Study Population

Inclusion Criteria: Adults (≥18 years), mechanically ventilated ≥48 hours, diagnosis of VAP based on clinical and radiological criteria, hemodynamically stable, and with normal renal function tests at enrollment; informed consent obtained from legal guardian/relative.

Exclusion Criteria: Cystic fibrosis, bronchiectasis, severe renal impairment or renal replacement therapy, known hypersensitivity to amikacin, or vasopressor requirement at enrollment.

6. Sample Size

A total of 180 patients (90 per group) were planned, assuming a 20% improvement in clinical outcomes with adjunctive therapy, 80% power, 5% significance level, and 10% anticipated dropout.

7. Randomization

Participants were randomized 1:1 using a computer-generated sequence, stratified by age, gender, and baseline SOFA score.

8. Interventions

Control Group (Group N): Empirical intravenous antibiotics (meropenem and moxifloxacin) per ICU protocol after collection of tracheal and blood cultures.

Intervention Group (Group A): Inhaled amikacin 20 mg/kg/day via nebulization in two divided doses, in addition to the same empirical intravenous antibiotics, initiated after culture collection.

9. Outcome Measures

Primary Outcome: Clinical improvement of VAP (Yes/No), defined by improvement in fever, oxygen requirement, leukocyte trend, and radiological infiltrates/consolidation.

Secondary Outcomes: Duration of mechanical ventilation (days), ICU length of stay (days), and adverse events.

10. Data Collection

Demographics, SOFA score, ventilation days, ICU stay, comorbidities, diagnostic criteria, microbiology, treatment regimens, and outcomes were recorded on a structured proforma and followed until ICU discharge or death.

11. Statistical Considerations (Summary)

Continuous variables were compared using independent t-tests; categorical outcomes using chi-square or Fisher's exact tests. Effect estimates included mean differences with 95% confidence intervals and odds ratios (95% CI) for binary outcomes. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS v26.

12. Ethical Considerations

Approved by the Institutional Review Board of PGMI (Ref No. 100/24) on 03 January 2024. Informed consent was obtained from the patient's legal guardian/relative. Confidentiality was maintained and data were de-identified.

13. Recruitment Status and Study Dates

Recruitment Status: Completed.
Study Start Date: 01 January 2024.
Primary Completion Date: 31 December 2024.
Study Completion Date: 31 December 2024.

14. Dissemination of Results

Results will be disseminated through peer-reviewed publications and scientific meetings; no identifiable data will be disclosed.

COVER PAGE

Official Title:

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

ClinicalTrials.gov Identifier:

NCT Number: Not yet assigned

Document Type:

Statistical Analysis Plan (SAP)

IRB Approval Reference:

IRB PGMI Ref No. 100/24

Date:

03 January 2024

Sponsor:

Lahore General Hospital / PGMI, Lahore, Pakistan

STATISTICAL ANALYSIS PLAN (SAP)

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods and procedures used to analyze data collected in this study. It is intended to support transparency and reproducibility for ethics and registry documentation.

2. Objectives and Endpoints

Primary Endpoint: Clinical improvement of VAP (Yes/No).

Secondary Endpoints: Duration of mechanical ventilation (days), ICU length of stay (days), and adverse events potentially related to inhaled amikacin.

3. Analysis Populations

Intention-to-Treat (ITT): All randomized participants analyzed according to assigned group, regardless of protocol deviations.
Per-Protocol (PP) (if applicable): Participants who received the allocated intervention and had evaluable outcomes; used for sensitivity analysis.

4. General Statistical Principles

All tests were two-sided with alpha=0.05. Continuous variables summarized as mean±SD (or median [IQR] if skewed). Categorical variables summarized as counts and percentages. Estimates reported with 95% confidence intervals.

5. Data Handling, Cleaning, and Coding

Data underwent range checks, consistency checks, and duplicate checks. Derived variables (e.g., durations) were computed using ICU logs. Any discrepancies were resolved by source verification. The final analysis dataset was locked prior to analysis.

6. Missing Data

The extent and pattern of missingness were assessed. If missingness was minimal, complete-case analysis was performed. If missingness exceeded a pre-specified threshold (e.g., >5% for a key outcome), sensitivity analyses were planned (best/worst-case for binary outcomes; multiple imputation for continuous outcomes), assuming missing at random where appropriate.

7. Primary Outcome Analysis

Clinical improvement (Yes/No) compared between groups using chi-square test; Fisher’s exact test used if expected cell counts <5. Effect measures: odds ratio (OR) with 95% CI. Additional measures (if reported): risk ratio (RR), risk difference (RD), and number needed to treat (NNT).

8. Secondary Outcomes Analysis

Duration of mechanical ventilation: Compared using independent t-test. Mean difference with 95% CI reported. Effect size reported as Cohen’s d (and Hedges’ g if desired).

ICU length of stay: Compared using independent t-test; mean difference with 95% CI and effect size

reported.

9. Assumptions and How They Were Verified

Normality: Shapiro–Wilk test and visual inspection (histograms/Q-Q plots).
Homogeneity of variance: Levene's test.
If assumptions were violated, non-parametric alternatives were planned (Mann–Whitney U for continuous outcomes) and/or robust methods (Welch t-test).

10. Multiplicity / Multiple Testing

The primary endpoint was tested at alpha=0.05 without adjustment. Secondary endpoints were interpreted as supportive/exploratory. If formal adjustment was required, a Holm–Bonferroni approach was pre-specified for the family of secondary endpoints.

11. Subgroup Analyses

Exploratory subgroup analyses planned by age category, sex, and baseline severity (SOFA score categories). Interaction testing was considered using logistic regression for the binary endpoint and linear models for continuous outcomes.

12. Sensitivity Analyses

Sensitivity analyses included per-protocol analysis, use of non-parametric methods where applicable, and analyses excluding extreme outliers to assess robustness.

13. Outliers and Influential Observations

Outliers assessed using boxplots and standardized z-scores. If influential observations were identified, analyses were repeated excluding those values, with both results documented.

14. Safety Analyses

Adverse events potentially attributable to inhaled amikacin (e.g., bronchospasm, transient desaturation during nebulization, renal function changes) were summarized by group. Comparisons used chi-square/Fisher's exact tests when appropriate; otherwise descriptive reporting was used.

15. Statistical Software

Primary analyses performed using SPSS version 26.0 (or later). Any additional computations (e.g., effect sizes) were verified with independent calculation.

16. SAP Deviations/Amendments

Any deviations from this SAP were documented with rationale, dated, and finalized before unblinding (if any) or prior to database lock.

17. Reporting

Results reported in accordance with CONSORT where applicable and in formats compatible with ClinicalTrials.gov results reporting requirements.

COVER PAGE

Official Title:

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

ClinicalTrials.gov Identifier:

NCT Number: Not yet assigned

Document Type:

Informed Consent Form (ICF)

IRB Approval Reference:

IRB PGMI Ref No. 100/24

Date:

03 January 2024

Sponsor:

Lahore General Hospital / PGMI, Lahore, Pakistan

INFORMED CONSENT FORM (ICF)

Clinical Outcomes of Inhaled Amikacin as an Adjunctive Therapy in Ventilator-Associated Pneumonia: A Prospective Randomized Comparative Study

1. Introduction

You are being asked to allow your relative to take part in a research study because they are critically ill in the ICU, are receiving mechanical ventilation, and have been diagnosed with ventilator-associated pneumonia (VAP). Please read this information carefully. Ask any questions you may have before signing.

2. Purpose of the Study

The purpose of this study is to determine whether inhaled amikacin, when added to standard intravenous antibiotics, improves recovery from ventilator-associated pneumonia.

3. Why Your Relative Is Being Asked to Participate

Your relative is eligible because they are 18 years or older, have been on a ventilator for at least 48 hours, and meet criteria for VAP.

4. Study Procedures

If you agree, your relative will be assigned by chance (randomly) to one of two treatment groups. One group receives standard intravenous antibiotics. The other group receives inhaled amikacin in addition to standard intravenous antibiotics. Blood and tracheal cultures will be collected as part of routine care.

5. Potential Benefits

Your relative may or may not benefit directly. Possible benefits include faster improvement in pneumonia and reduced time on the ventilator. The information gained may help improve treatment for future patients.

6. Risks and Discomforts

Inhaled amikacin is generally well tolerated. Possible risks include cough, wheeze/bronchospasm, or temporary drop in oxygen saturation during nebulization. Although inhaled delivery reduces systemic exposure, kidney-related side effects are still monitored, especially if other nephrotoxic medicines are used.

7. Alternatives

Your relative will continue to receive standard ICU care for VAP even if you do not allow participation in this study.

8. Confidentiality

All information will be kept confidential. Data will be coded and stored securely. Results may be published, but no information that could identify your relative will be shared.

9. Voluntary Participation and Right to Withdraw

Participation is voluntary. You may withdraw consent at any time without affecting the quality of medical care your relative receives.

10. Costs and Compensation

There is no additional cost to you for participation. No monetary compensation is provided.

11. Ethical Approval

This study was approved by the Institutional Review Board of PGMI (Ref No. 100/24) on 03 January 2024.

12. Contact Information

If you have questions about the study or your relative's rights as a participant, you may contact the Principal Investigator, Department of Anaesthesia, Lahore General Hospital.

13. Consent Statement

I have read (or had read to me) the information above. I have had the opportunity to ask questions and received satisfactory answers. I voluntarily agree for my relative to participate in this study.

14. Signatures

Name of Patient: _____
Hospital MR No.: _____

Name of Legal Guardian/Relative: _____
Relationship to Patient: _____
Signature/Thumb Impression: _____
Date: _____

Name of Witness: _____
Signature of Witness: _____
Date: _____

Name of Person Obtaining Consent: _____
Signature: _____
Date: _____