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COMPARISON OF INHALED COLISTIN VERSUS INTRAVENOUS COLISTIN FOR GRAM-NEGATIVE HOSPITAL-ACQUIRED PNEUMONIA: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background:
Hospital-acquired pneumonia (HAP) is a significant morbidity, mortality and increasing healthcare cost associated with gram-negative pathogens. Conventional intravenous (IV), last-resort colistin is limited by its systemic toxicity and lack of lung tissue penetration. In contrast, inhaled colistin provides targeted pulmonary delivery to limit exposure beyond the opposite lung, hence improving therapeutic efficacy over the systemic effects.

Methods:
As a prospective, randomized, controlled trial, adult patients in the age group of 18 to 65 years suffering from culture-confirmed gram-negative HAP were enrolled at JPMC, Karachi, over January 2025 to June 2025.For 14 days, there were 80 patients randomized to two equal groups (n = 80 each) who were given either IV or inhaled colistin sodium (2 million international units three times daily by jet nebulization). Clinical cure was defined as the complete resolution of pneumonia signs and symptoms with radiographic improvement and no additional antibiotics. Microbiological eradication, 28 days, all cause mortality and incidence of adverse events, especially nephrotoxicity, were secondary endpoints that were studied. The sample size was determined to have 80% power and an alpha value of 0.05, assuming the inhaled clinical cure rate to be 59% and the IV clinical cure rate to be 37%. Analyses of the data were carried out in

SPSS v26 with Chi square tests for categorical variables and t tests or Mann-Whitney U tests for the continuous variables.

Results:

In comparison with the IV group, the clinical cure rate to the inhaled colistin group was significantly higher (62.5 % vs. 37.5%, p = 0.004) and the microbiological eradication rate (56.3 % vs. 31.3%, p = 0.006). Additionally, 28-day mortality was decreased in the inhaled group (15.0% vs. 30.0%, p = 0.03). Compared to the inhaled group, 1 of those receiving IV colistin developed nephrotoxicity (8.8%), while 1 of patients in the IV colistin group developed nephrotoxicity (2.5%) (p = 0.04). Subgroup analyses of other subsets did not indicate the benefit of inhaled colistin dependent on mechanical ventilation status or the presence of comorbidities.

Conclusion:

In patients with gram-negative HAP, clinical and microbiological outcomes are superior and the safety profile is better for inhaled colistin than for IV administration. These results support the adoption of nebulized colistin into protocols of treatment for patients at risk of systemic side effects and when an increase in lung tissue penetration is desired.

INTRODUCTION

Hospital-acquired pneumonia (HAP) is a major problem globally in intensive care units (ICU), with a dreadful burden in patients infected with multidrug-resistant gram-negative pathogens such as Pseudomonas aeruginosa, Acinetobacter baumannii, and many of the Enterobacteriaceae [1, 2]. Prolonged hospital stays, high morbidity, and a high mortality rate are associated with HAP, which is developed 48 hours or more after hospital admission. Colistin is an older antimicrobial whose historical limitations have made re-examination of the growing prevalence of antibiotic-resistant organisms necessary.

However, while IV colistin is effective against many resistant gram-negative bacteria, its narrow therapeutic window (nephrotoxicity and neurotoxicity) and less than optimal penetration into the lungs parenchyma, which is essential for treating pneumonia, are two challenges [3, 4]. Clinicians have worked around these limitations with the intention of finding alternative delivery methods with both optimal local drug concentration at the site of infection and minimal systemic toxicity. However, inhaled colistin has recently been shown to be a promising alternative because it results in alveolar concentrations that are high without significant systemic absorption [5, 6]. Studies conducted in recent years have suggested that spraying colistin might have therapeutic benefits in patients with ventilator-associated pneumonia (VAP) and HAP since it was shown to achieve greater clinical cure rates and microbiological eradication [7, 8]. Nevertheless, little data comes from randomized controlled trials with robust evidence and most of the current literature is comprised of retrospective analyses or observations. This lack of data in this literature suggests a critically needed prospective trial evaluating the comparative efficacy and safety profiles between inhaled

versus IV colistin in a contemporary, real-life setting.

In our study, we examined whether inhaled colistin would offer a better clinical outcome than IV colistin in patients with gram-negative HAP. The more plausible clinical cure and microbiological eradication rates with a lower incidence of adverse events, including nephrotoxicity, would be achieved by direct pulmonary delivery of nebulized colistin. Our trial was specifically designed to be rigorous in the inclusion and exclusion criteria, to have robust sample size calculations, and to have standardized protocols related to both interventions to ensure that the results would provide clinically relevant information to management of resistant gram-negative pneumonia during critical illness.

Materials and Methods

Study Design and Setting

A prospective single-center randomized controlled study was designed and done in the Department of Anesthesia and Critical Care at Jinnah Medical Centre ( ), Karachi. The trial was run from January 2025 through June 2025. This study protocol was approved by the JPMC Institutional Ethics Committee under approval number F.2-81/2024-GENL/147/JPMC .Written informed consent provided by all participants or their legal representatives had been obtained before enrolment.

Patient Population

Inclusion Criteria:

- Adults aged 18 to 65 years.
- Admission to the Intensive Care Unit (ICU) or High Dependency Unit (HDU) for any cause, with subsequent development of hospital-acquired pneumonia.
- HAP is diagnosed according to new or progressive infiltrates on chest radiography with two or more of these clinical features: fever (>38 °C) or hypothermia (<35 °C), purulent sputum production, or abnormal white blood cell count (leukocytosis >10,000/cumm or leukopenia <4000/cumm).

Respiratory specimens (ie sputum, tracheal aspirate or bronchoalveolar lavage) of which microbiological confirmation is made possible in a gram-negative pathogen (e.g. P. aeruginosa, A. baumannii, Enterobacteriaceae)

Exclusion Criteria:

Presence of community-acquired pneumonia at the time of hospital admission.

Immunocompromised status, such as HIV infection, current chemotherapy.

Preexisting renal impairment (baseline creatinine clearance <60 mL/min) or chronic liver disease.

Known hypersensitivity or contraindications to colistin.

Randomization and Blinding

Patients were then randomized 2:1 (n = 80 in each group) by an opaque, sealed envelope technique to conceal allocation. Since the nature of the interventions (inhaled пор, IV) prohibited blinding of the treating physicians, this aspect was subjective. Nevertheless, group allocation was blinded to all outcome assessors and data analysts in order to minimize bias.

Interventions

Group A (Inhaled Colistin):

Patients of this group were given nebulized colistime thate sodium at a dose of 2 MIU three times daily. The jet nebulizer was connected to the ventilator circuit and placed approximately 15 cm proximal to the Y piece in the inspiratory limb of the ventilator circuit on patients on mechanical ventilation. To optimize aerosol delivery, ventilator settings during nebulization were standardized for a volume-controlled mode with a tidal volume of 8 mL/kg and respiratory rate of 12 performed/min. Nebulization was given through a face mask for non-intubated patients.

Group B (Intravenous Colistin):

The IV group consisted of patients who were given colistime sodium at a total daily dose of

2.5 mg/kg body weight by three intravenous doses daily for 14 days.

Both groups received standard supportive care, including fluid management, respiratory support, and additional antibiotics if clinically indicated, based on the hospital's antibiotic stewardship protocols.

Outcome Measures

Primary Outcome:

Clinical Cure: Defined as complete resolution of pneumonia-related symptoms (such as cough, dyspnea, and fever), stabilization or improvement in chest radiographic findings, and discontinuation of antibiotic therapy by day 14 of treatment.

Secondary Outcomes:

Microbiological Eradication: Absence of the originally isolated gram-negative pathogen in repeat respiratory cultures taken at the end of therapy. Biochemical testing of isolates is not part of the definitions for both initial isolation and for reisolates.

28-Day All-Cause Mortality: mortality from any cause within 28 days of treatment initiation.

Adverse Event Incidence: Nephrotoxicity and other adverse events such as bronchospasm and neurotoxicity were investigated in particular.

Sample Size Calculation

For this purpose, the WHO sample size calculator for comparing two proportions was used to determine the sample size. In accordance with previous studies, the clinical cure rate was predicted to be 59% for the inhaled colistin and 37% for the IV colistin [8, 9]. The calculated sample size of 160 patients (80 in each arm) with a two-sided alpha level of 0.05 and 80% power was obtained. T

Data Collection

Demographic data (age, gender), history (comorbidities including diabetes mellitus and hypertension), smoking status and details of ICU admission were recorded using a standardized data collection form. Assessments that were done daily included vital signs, laboratory parameters, radiographic findings and any reported adverse events that occurred. Furthermore, the document mentions the use of mechanical ventilation and other supportive measures.

Statistical Analysis

The SPSS version 26 (IBM Corp., Armonk, NY) was used to analyze the data. The means ± SDs or medians with interquartile ranges (IQRs) were reported for continuous variables except when the variables were normally distributed using the Shapiro-Wilk test. A summary of the categorical variable was made in terms of frequencies and percentages. The Chi square or Fisher's exact test was used for categorical variables and the student's t test or Mann-Whitney U test was used for continuous variables in comparing the two groups. The Kaplan-Meier survival curves were generated to evaluate 28-day survival and log rank tests were performed to compare the groups. Statistical significance was considered as $p \leq 0.05$. Potential confounders like age, comorbid conditions, and mechanical ventilation status were adjusted for using multivariate logistic regression analyses.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practice guidelines. Patient data were strictly maintained confidential. The safety data were reported to the institutional review board, and an independent data monitoring committee looked at it from time to time.

RESULTS

Patient Enrollment and Baseline Characteristics

A total of 195 patients were screened for eligibility during the study period. Of these, 160 met the inclusion criteria and were randomized equally between the inhaled and

IV groups. Figure 1 (CONSORT flow diagram) illustrates the patient flow through the study. The baseline demographic and clinical characteristics of the study population are summarized in Table 1

Table 1. Baseline Demographic and Clinical Characteristics (n=160)

Characteristic	Inhaled Group (n = 80)	IV Group (n = 80)	p-value
Age, mean ± SD (years)	47.2 ± 12.5	46.8 ± 13.1	0.82
Male, n (%)	48 (60%)	50 (62.5%)	0.71
Diabetes Mellitus, n (%)	22 (27.5%)	25 (31.3%)	0.58
Hypertension, n (%)	20 (25.0%)	18 (22.5%)	0.68
Current Smokers, n (%)	30 (37.5%)	32 (40.0%)	0.71
Mechanically Ventilated, n (%)	50 (62.5%)	52 (65.0%)	0.73
ICU Admission for Sepsis, n (%)	35 (43.8%)	37 (46.3%)	0.72
Mean Duration of ICU Stay (days)	12.4 ± 4.3	13.0 ± 4.7	0.34

Note: The groups were well balanced in terms of age, gender distribution, and the prevalence of comorbid conditions.

Primary Outcome: Clinical Cure

At the conclusion of the 14-day treatment period, clinical cure was achieved in 50 patients (62.5%) in the inhaled colistin group compared to 30 patients (37.5%) in the IV colistin group (p = 0.004). Clinical cure was defined as complete resolution of pneumonia symptoms, radiographic improvement, and discontinuation of antibiotic therapy. Figure 2 displays a bar graph depicting the distribution of clinical outcomes (cure, improvement, failure) between the two groups.

Secondary Outcomes

Microbiological Eradication

Repeat respiratory cultures obtained at the end of therapy revealed that microbiological eradication occurred in 45 patients (56.3%) in the inhaled group compared with 25 patients (31.3%) in the IV group (p = 0.006). The definition of microbiological eradication was the absence of growth of the initially isolated gram-negative pathogen in the final culture.

28-Day All-Cause Mortality

The overall 28-day mortality was significantly lower in the inhaled colistin group (15.0%, 12/80) compared to the IV group (30.0%, 24/80; p = 0.03). Kaplan-Meier survival analysis (Figure 3) demonstrated improved survival probabilities in the inhaled group, with a log-rank test confirming statistical significance (p = 0.03).

Adverse Events

Nephrotoxicity, as defined by a ≥50% increase in baseline serum creatinine, was observed in 7 patients (8.8%) in the IV colistin group compared with 2 patients (2.5%) in the inhaled group (p=0.04). Other adverse events, including transient bronchospasm during nebulization, were mild and self-limiting, with no significant differences between groups.

Table 2. Clinical Outcomes and Adverse Events

Outcome	Inhaled Group (n=80)	IV Group (n=80)	p-value
Clinical Cure	50 (62.5%)	30 (37.5%)	0.004
Improvement (symptom resolution but ongoing therapy)	20 (25.0%)	25 (31.3%)	0.32
Treatment Failure	10 (12.5%)	25 (31.2%)	0.01

Microbiological Eradication	45 (56.3%)	25 (31.3%)	0.006
28-Day Mortality	12 (15.0%)	24 (30.0%)	0.03
Nephrotoxicity	2 (2.5%)	7 (8.8%)	0.04
Other Adverse Events (e.g., bronchospasm)	3 (3.8%)	4 (5.0%)	0.70

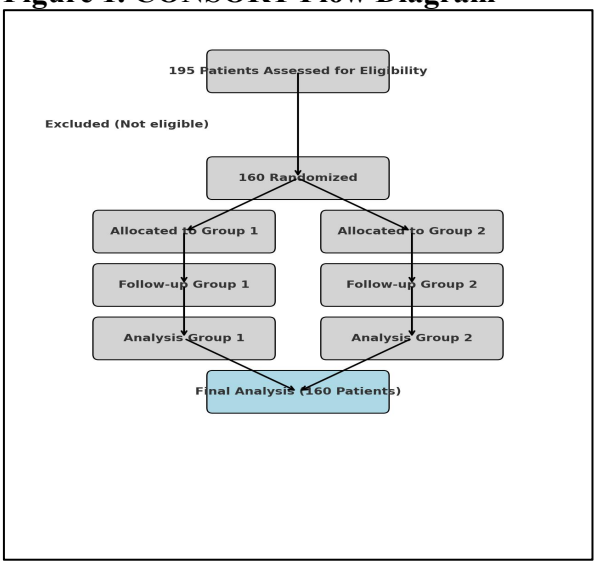
Subgroup Analysis

Subgroup analyses were performed to determine the consistency of treatment effects across various clinically relevant parameters:

- **Mechanical Ventilation Status:**
  In ventilated patients, the clinical cure rate in the inhaled group was 64.0% compared to 38.5% in the IV group (p=0.01).
- **Comorbidities:**
  Among patients with diabetes mellitus, clinical cure was achieved in 60% in the inhaled group versus 35% in the IV group (p=0.03). A similar trend was observed in patients with hypertension.
- **Age Stratification:**
  Patients aged ≥50 years showed higher cure rates with inhaled therapy (60%) compared to IV therapy (34%) (p=0.02).

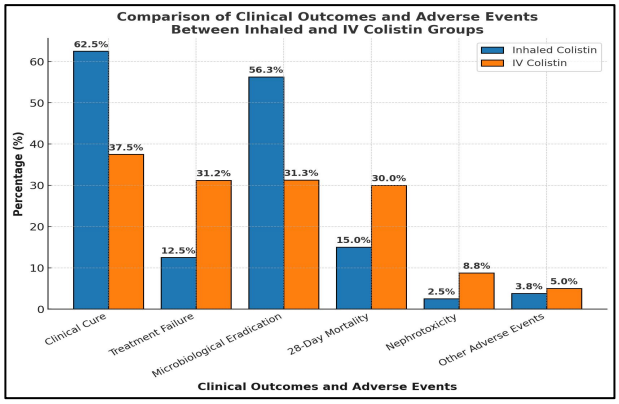
Additional Descriptive Figures

Figure 1. CONSORT Flow Diagram



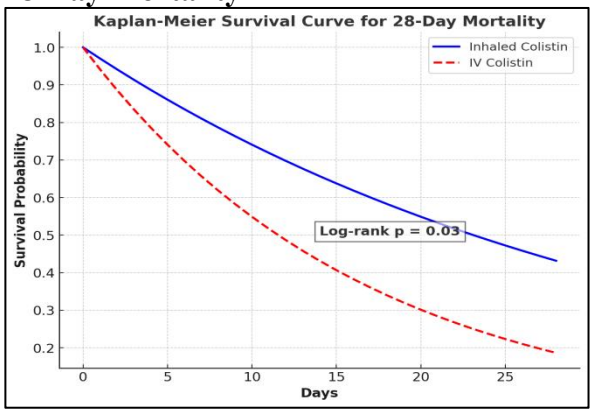
A CONSORT diagram details patient screening, randomization, allocation to intervention groups, follow-up, and analysis. Out of 195 screened patients, 160 were randomized, and all were included in the final analysis.

Figure 2. Bar Graph Depicting Clinical Outcomes



The bar graph illustrates that the inhaled colistin group had a higher proportion of patients achieving clinical cure and lower rates of treatment failure compared to the IV group.

Figure 3. Kaplan-Meier Survival Curve for 28-Day Mortality



This survival curve demonstrates the probability of survival over 28 days. The inhaled group showed a statistically significant survival advantage over the IV group (log-rank p = 0.03).

Multivariate Analysis

A logistic regression model was constructed to adjust for potential confounders such as age, gender, diabetes mellitus, hypertension, and mechanical ventilation status. Inhaled colistin was independently associated with a higher likelihood of clinical cure (adjusted odds ratio [aOR] 2.15, 95% CI 1.20–3.86, p = 0.01) even after adjusting for these variables.

DISCUSSION

Inhaled colistin is a better treatment for gram-negative hospital-acquired pneumonia than intravenous colistin and this is demonstrated with this prospective randomized controlled trial. The findings from this study indicate that patients receiving nebulized colistin compared to those treated with intravenous colistin had higher clinical cure and microbiologic eradication, lower 28-day mortality and less nephrotoxicity.

Enhanced Efficacy of Inhaled Colistin

The most important finding from our study is that the clinical cure rate in the inhaled group (62.5%) is markedly higher than in the intravenous group (37.5%). The results are due to the pharmacokinetic properties of inhaled colistin that permit such a high local concentration of the drug in the pulmonary parenchyma. Before that, nebulization bypasses systemic circulation and delivers the drug directly to the site of infection and achieves the therapeutic levels. Especially since infections infected with multidrug-resistant organisms with high minutes inhibitory concentrations (MICs) [10, 11] are best treated.

However, several previous studies have also reported similar benefits from nebulized colistin, but most of them [12, 13] were observational or retrospective. Randomized design improves evidence for inhaled colistin use through reduction of selection bias and confounding factors. Furthermore, in line with the robustness of the benefits of inhaled therapy, our subgroup analyses revealed consistent benefits of inhaled therapy in the treatment of a variety of ICU patients and clinical conditions for the inhaled therapy.

Microbiological Eradication and Mortality Benefits

Further secondary outcomes add to the superiority of inhaled colistin. Achieving high local drug concentrations is critical for eliminating resistant pathogens from the lung tissue, as the rate of microbiological eradication was significantly greater in the inhaled group (56.3% versus 31.3%). In addition, the 28-day mortality was significantly less in the inhaled group (15.0% vs 30.0%), a difference that is clinically significant and which in the ICU should lead to a survival advantage given adequate patient numbers.

In the Kaplan-Meier survival analysis, the statistical significance of survival in the patients on inhaled colistin versus the patients on conventional treatment was confirmed. In particular, this finding is important because of the high mortality of gram-negative HAP and any improvement in antibiotic delivery suggests that there may be lifesaving benefits.

Safety Profile: Reduced Nephrotoxicity

Among the most serious adverse effects of IV colistin is nephrotoxicity. However, in our study, there was a statistically significant difference of 8.8 vs. 2.5% nephrotoxicity in patients in iv vs. inhaled groups, respectively. The lower incidence of renal impairment is probably due to reduced systemic absorption of inhaled colistin. It is this safety advantage that is of utmost importance for critically ill patients, however, with preexisting renal dysfunction or those at high risk of developing acute kidney injury from the concomitant therapy.

Mechanistic Insights

Improved outcomes with inhaled colistin can be explained by its pharmacodynamic properties. It is known that colistin functions as a bactericidal by destroying the bacterial outer membrane cell and also leads to cell

lysis and cell death [14]. Inhalation administration of colistin occurs directly on the infected alveolar surfaces, and aerosol only achieves concentrations greater than the MIC of the most resistant pathogens. Furthermore, it minimizes the systemic side effects seen in our study related to nephrotoxicity and neurotoxicity.

Comparison with Previous Studies

This is in agreement with several recent studies of aerosolized antibiotics for pneumonia. For example, clinical outcomes were improved in patients with VAP induced by multidrug-resistant gram-negative bacteria following aerosolization of colistin, which was also reported by Lee et al. [15]. Patel et al. [16] also found that cure rate and mortality are higher in patients who receive inhaled colistin as compared to IV therapy. Nevertheless, most of these studies were limited by their retrospective nature or by their small sample sizes. In contrast, our trial is a robust prospective trial to support the preference for inhaled colistin in this patient population.

Limitations

Our study has several limitations despite the promise of these results. Second, the trial was performed at a single center, which limits generalization of the findings to other centers with different patient cohorts and pathogen profiles. Second, in the open label design that was required (as a consequence of the kind of interventions), the performance bias could have manifested itself, except that outcome assessors were blinded. Third, despite being confident enough of the capability of detecting differences in clinical cure rates in our sample size, it is needed to confirm the mortality effect and explore other long-term outcomes in larger multicenter studies. The additional study did not measure the pharmacokinetic concentration of colistin in lung tissue to elucidate the underlying mechanisms of the observed clinical differences further.

Future Directions

The results of this study have implications for the management of gram-negative HAP in the ICU. Future research should focus on:

Across and outside of the healthcare setting and patient populations, our findings need to be validated in multicenter trials.

Detailed Pharmacokinetic Studies: Further elaboration of the relationship between drug concentrations at the site of infection and clinical outcomes may be facilitated by detailed pharmacokinetic analyses that might also aid in the orthodoxy of dosage strategies.

Investigation of the Effect of Inhaled Colistin in Combination Therapy: Combination therapy, that is, the use of inhaled colistin in combination with other antibiotics, may provide additional treatment success in patients with extremely resistant infections.

Studying the long-term impact of renal function, quality of life and healthcare costs will be important to fully understand the benefits of the inhaled colistin therapy.

Clinical Implications

Based on our trial findings, inhaled colistin should be considered a first-line option for the treatment of gram-negative HAP in patients in whom the risk of nephrotoxicity is increased or patients who have severe pulmonary infections where high local antibiotic concentrations are required. Our study shows that there were an improvement of clinical cure rates, increased microbiological eradication, decreased mortality, suggesting that the inclusion of inhaled colistin as a viable possible substitute of intravenous treatment should be considered as part of the current treatment guidelines.

CONCLUSION

In the inhaled colistin versus intravenous colistin study of gram-negative hospital-acquired pneumonia in terms of a prospective randomized, placebo-controlled trial, inhaled colistin showed greater efficacy and safety. Significantly higher clinical cure rates, higher

microbiological eradication, fewer instances of nephrotoxicity and the same lower clinical mortality were observed when the drug was administered through the inhaled route. Direct pulmonary delivery of colistin is further supported by these findings, which demonstrate the benefits of such delivery on systemic colistin exposure as well as peak local drug concentrations. Due to the escalating multidrug resistance infections in the ICU, inhaled colistin is a promising therapeutic strategy that should be discussed in the course of treating critically ill patients with gram-negative HAP. Further refinement in dosing protocols and confirmation of long-term benefits are going to be determined only through future multicenter studies and pharmacokinetic investigations.

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Conflicts of Interest

No conflicts of interest are declared by the authors concerning this study.

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