BRIEF RESEARCH COMMUNICATION

Polymyxin B Plus Aerosolized Colistin vs Polymyxin B Alone in Hospital-acquired Pneumonia ("AEROCOL" Study): A Feasibility Study

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Received on: 13 June 2024; *Accepted on*: 10 July 2024; *Published on:* 31 July 2024

Abstract

Introduction: In hospital-acquired pneumonia (HAP) due to extensively drug resistant gram-negative pathogens, can treatment with high-dose colistin aerosolization using specific aerosol delivery protocol, improve clinical outcome in addition to systemic polymyxin-B?

Materials and methods: In a randomized control trial, invasively ventilated adult ICU patients with HAP in whom clinicians decided to start systemic polypeptide antibiotics, were randomized to receive either intravenous polymyxin-B plus high-dose colistin nebulization (5-MIU 8-hourly) using specific protocol or intravenous polymyxin-B alone.

Results: The study was closed early after recruiting 60% of planned patients because of slow rate of recruitment (24 patients in over 30 months). Treatment success (Primary outcome) was nonsignificantly higher in intervention group (63.66 vs 30.77%; $p = 0.217$). There was higher rate of microbiological cure in intervention group (60 vs 9.09%: $p = 0.018$). Numerically better secondary outcomes including fever-free days, ventilator- or vasopressor free days at day-7, ICU and hospital mortality also did not reach statistical significance. Two episodes of transient hypoxia were seen during aerosol delivery. However, overall incidences of adverse effects were not different between groups.

Conclusion: This study could not confirm superiority of high-dose colistin aerosolization plus systemic polymyxin-B strategy over polymyxin-B alone in treating HAP due to extensive drug resistance (XDR) gram-negative pathogens.

Keywords: Aerosolized colistin, Extensive drug resistance, Gram negative pathogens, Hospital-acquired pneumonia, Polymyxin-B.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24767

Highlights

- In this randomized trial, we looked for the superior clinical efficacy of systemic polypeptide plus aerosolized colistin delivered in a protocolized way compared to systemic polypeptide alone, in patients with hospital-acquired pneumonia (HAP) related to extensively drug resistant gram-negative pathogens.
- The study was prematurely terminated after recruiting 60% of proposed sample size.
- There was a strong but statistically nonsignificant trend towards favorable outcome in the intervention group in all clinical parameters evaluated.
- No serious adverse effects were observed in the intervention group.

Introduction

Antibiotic prescription in HAP is getting increasingly complicated with rising isolation of extensive drug resistant (XDR) gram-negative pathogens, frequently sensitive only to polypeptide antibiotics (colistin or polymyxin-B).[1] Despite having excellent activity *in vitro* against gram-negative organisms, treatment of pneumonia with polypeptide antibiotics is limited by poor lung tissue penetration.[2,3] A potential way to achieve higher concentration of colistin (as well as perhaps polymyxin-B) in the lung tissue is to deliver the drug by aerosolized route. The aerosolized route also has the potential advantage of reducing the systemic toxicities of polypeptides, including nephrotoxicity and neurotoxicity. Unfortunately, clinical studies have failed to confirm these potential benefits unequivocally.[4,5] However, all these studies are limited substantially by one or more of several factors. Firstly, the dose of colistin used is often inadequate to achieve the required lung tissue concentration.[2,5] Secondly, jet and ultrasonic nebulizers used in many of these studies have important limitations in terms of the delivery of aerosolized antibiotics to lung tissue.[6] Thirdly, most of these studies failed to specify about the ventilator setting used during aerosol delivery, that may have a significant impact on the lung tissue concentration of colistin.[7] Fourthly, in some studies, patients were randomized only after identification of the causative pathogen, potentially delaying effective antimicrobial therapy.[8] Finally, there is a questionable rationale for adding aerosolized colistin in the absence of beta-lactam resistance, as applied in some studies.[8]

We designed a pilot study to look at the clinical efficacy of high-dose colistin aerosolization in treating HAP. We hypothesized that in patients with HAP caused by suspected or confirmed carbapenemase

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How to cite this article: Ghosh S. Polymyxin B Plus Aerosolized Colistin vs Polymyxin B Alone in Hospital-acquired Pneumonia ("AEROCOL" Study): A Feasibility Study. Indian J Crit Care Med 2024;28(8):792–795.

Source of support: Nil

Conflict of interest: None

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producing gram-negative pathogens, administration of aerosolized colistin via vibrating mesh nebulizer and standardized ventilator settings plus intravenous polymyxin-B will have better treatment success compared to intravenous polymyxin-B alone.

Materials and Methods

The study was conducted in the 18-bed mixed ICU of Fortis-Escorts Hospital, Faridabad, Haryana. It was approved by Institutional Ethics Committee (EC/2021/27 dated 07-07-2021) and was registered with Clinical Trial Registry of India (CTRI/2021/7/034866).

Patients

Adult patients (18 years) with clinical evidence of HAP on invasive mechanical ventilation, in whom treating clinician planned to initiate intravenous polymyxin-B (empirically or definitive), were included in the study. Patients requiring intravenous polypeptide antibiotics for other indication or those with known hypersensitivity to colistin or lack of clinical equipoise amongst treating clinicians or pregnant ladies and refusal of consent were excluded from the study.

Study Procedure

All eligible and consenting patients were randomized to receive either polymyxin-B alone or polymyxin-B plus aerosolized colistin. Randomization was done through a computer-generated randomization table using an opaque envelope to conceal. A patient was randomized only once during their hospital stay.

Colistin Aerosolization

Aerosolized colistin at a dose of 5 MIU every 8 hours was delivered with a vibrating mesh nebulizer (Aeroneb Pro®, Aerogen Nektar Corporation, Galway, Ireland) positioned on the inspiratory limb 20 cm proximal to the Y-piece.[6,9] Specific ventilator settings were used during the aerosolization period: volume control mode with constant flow and tidal volume of 8 mL/kg predicted body weight, respiratory rate of 12/minute, inspiratory/expiratory ratio of 1:1, inspiratory pause of 20%. Strict synchrony between patient and ventilator was maintained throughout aerosolization (sedation with propofol, if necessary).[7] Both active and passive humidification measures were discontinued during aerosolization. Servo Duo Guard filter (Maquet Critical Care AB, Rontagen Vegen 2, SE-17154 Solna, Sweden) was positioned on the distal part of the expiratory limb. After each aerosolization period, prior ventilator setting and humidification measures were restored. Aerosolized colistin was continued till extubation or till clinician decided to discontinue polypeptides, or up to a maximum period of 14-days.

Intravenous Polymyxin B

Polymyxin-B was administered at 30,000 IU/kg of total body weight (TBW) in three divided doses, following a loading dose of 20,000 IU/kg TBW.[10] Duration of intravenous polymyxin-B was based on pathogen type, clinical improvement, including serial procalcitonin measurements, up to a maximum duration of 14-days.

Additional antibiotics prescription was at the discretion of the clinician. Two sets of blood samples (10 mL each) and bronchoalveolar lavage (BAL) fluid were sent for culture before starting antibiotics. De-escalation was done whenever feasible.

Outcome Measures

Primary outcome of the study was the percentage of patients with "Treatment Success", defined as either clinical cure or clinical improvement with evidence of microbiological clearance whenever applicable. Clinical cure was defined as complete resolution of all clinical signs and symptoms of pneumonia, along with improvement of abnormalities in chest imaging. Clinical improvement was defined as significant improvement of clinical signs and symptoms of pneumonia along with at least a lack of progression of abnormalities in chest imaging, before being shifted out of the ICU or before death from unrelated causes.

Secondary outcome measures were rate of microbiological clearance, fever-free days at day-7, ventilator or vasopressor-free days at day-7, ICU and hospital mortality, ICU and hospital length of stay, adverse effects of aerosolized colistin or need for new RRT throughout treatment period.

Sample Size

In the absence of any prior data, we decided to include a convenient sample size of 40 patients (20 in each arm).

Results

The study was discontinued early, in view of slow rate of recruitment, vide Institutional Ethics Committee letter number EC/2024/40 dated 03-06-2024. Only 24 patients could be recruited over 30 months period (first patient recruited on 21 October 2021)—11 of them were randomized to intervention group and 13 to control group.

Baseline characteristics were similar between the two groups (Table 1). 16 of 24 patients could be classified as having ventilator-associated pneumonia (VAP). Bronchoalveolar lavage culture was positive in 21 patients; all growing gram-negative pathogens, 20 of them being carbapenemase positive. All patients received initial appropriate antibiotic. 6 patients in the intervention group and 10 patients in the control group received the additional antibiotics. Details of microbiological and additional antibiotic prescription data are provided in the Supplementary Tables 1 and 2.

Outcome

There was a higher rate of treatment success in the intervention group (63.66 vs 30.77%). However, the difference did not reach statistical significance (Table 2). Protocol violation was seen in one of the patients in the intervention group, as aerosolized colistin could be delivered only after 24-hours of randomization. There was no significant difference in treatment success even after exclusion of this patient (70% in intervention vs 30.77% in control: $p = 0.1$).

Microbiological clearance was significantly higher in intervention group (60 vs 9.09%: $p = 0.018$). There were no significant between group differences in other secondary outcome measures.

Adverse Effects

Two episodes of transient hypoxia were reported during aerosol delivery. However, aerosol delivery was not complicated by any episode of bronchospasm, expiratory filter block or hypotension. None of the patients required new renal replacement therapy post-randomization.

Discussion

Despite strong trend towards favorable outcomes in the intervention group (aerosolized colistin plus polymyxin-B), our study was inadequately powered to confirm the significance of these findings. However, we observed a significantly higher

Table 1: Comparison of baseline characteristics between intervention and control groups

Parameters	*Intervention (n = 11)*	*Control (n = 13)*	*Total (n = 24)*	*p-value*
Age	66.09 ± 7.63	65.08 ± 15.54	65.54 ± 12.31	0.838†
Gender				
Female	3 (27.27%)	3 (23.08%)	6 (25%)	1*
Male	8 (72.73%)	10 (76.92%)	18 (75%)	
Admission type				
Medical	10 (90.91%)	12 (92.31%)	22 (91.67%)	1*
Surgical	1 (9.09%)	1 (7.69%)	2 (8.33%)	
Charlson comorbidity	6 (4.5–8)	3 (3–8)	5.5 (3–8)	0.465‡
Diabetes mellitus	6 (54.55%)	3 (23.08%)	9 (37.50%)	0.206*
Chronic kidney disease	2 (18.18%)	2 (15.38%)	4 (16.67%)	1*
Chronic liver disease	1 (9.09%)	2 (15.38%)	3 (12.50%)	1*
Chronic heart failure	1 (9.09%)	3 (23.08%)	4 (16.67%)	0.596*
Chronic lung disease	0 (0%)	1 (7.69%)	1 (4.17%)	1*
Neuromuscular	8 (72.73%)	5 (38.46%)	13 (54.17%)	0.123*
Immunocompromised	1 (9.09%)	1 (7.69%)	2 (8.33%)	1*
APACHE II score	26.18 ± 7.59	25.46 ± 6.92	25.79 ± 7.08	0.81†
SOFA score	9.82 ± 2.14	10.23 ± 3.77	10.04 ± 3.07	0.751†
Septic shock	5 (45.45%)	10 (76.92%)	15 (62.50%)	0.206*
PaO_2/FiO_2 ratio (mm Hg)	124.64 ± 40.19	164.38 ± 86.48	146.17 ± 70.81	0.157†
Lactate (mmol/L)	1.8 (1.4–2.5)	1.4 (1–2.3)	1.5 (1–2.45)	0.309‡
Total leukocyte count (mm^3)	19772.73 ± 9551.14	18846.15 ± 5209.86	19270.83 ± 7351.63	0.766†
Procalcitonin (ng/mL)	3.8 (2.7–9.4)	4.8 (2.4–6.6)	4.7 (2.47–8.82)	0.486‡

†Independent *t*-test; ‡Mann–Whitney test; *Fisher's exact test

Table 2: Comparison of outcomes between intervention and control groups

Outcome	*Intervention (n = 11)*	*Control (n = 13)*	*Total (n = 24)*	*p-value*
Primary outcome				
Treatment success	7 (63.64%)	4 (30.77%)	11 (45.83%)	0.217*
Secondary outcomes				
Microbiological cure	6 (60%)	1 (9.09%)	7 (33.33%)	0.018*
Fever-free days at day 7	5 (0–5.5)	0 (0–5)	0 (0–5)	0.078‡
Ventilator-free days at day 7	0 (0–3.5)	0 (0–4)	0 (0–4)	0.738‡
Vasopressor-free days at day 7	5 (0.5–6.5)	0 (0–5)	5 (0–5.25)	0.08‡
ICU mortality	5 (45.45%)	10 (76.92%)	15 (62.50%)	0.206*
Hospital mortality	6 (54.55%)	10 (76.92%)	16 (66.67%)	0.39*
ICU length of stay (Days)	16 ± 9.37	10.46 ± 6.19	13 ± 8.13	0.097†
Hospital length of stay (Days)	20.36 ± 7.63	13 ± 7.4	16.38 ± 8.25	0.026†

†Independent *t*-test; ‡Mann–Whitney test; *Fisher's exact test

microbiological clearance in the intervention group. This finding correlates with earlier studies.[4,5,8,9]

Our study has several methodological strengths compared to earlier studies. Firstly, we administered intravenous polymyxin-B very early in both groups as the majority of respiratory pathogens isolated from respiratory samples from our ICU patients are carbapenemase producing gram-negative rods, mostly sensitive to polypeptide antibiotics alone (data presented in the Annual Conference of European Society of Intensive Care Medicine in Milan, 2017). This was reconfirmed in the present study too. Polymyxin-B has certain advantageous pharmacokinetic over colistin including achieving faster steady-state plasma concentration and a lack of renal dose modification.[11] Recent consensus guideline also recommends polymyxin-B over colisitn for systemic treatment of most infections including lung.[10] Secondly, we used aerosolized colistin at a dose of 15 MIU in three divided doses. In experimental pneumonia model in piglets, colistin lung tissue concentration could reach a level above MIC breakpoint only at a dose of 16 mg/kg of colistimethate sodium.[3] If transmitted for a 75 kg adult, the dose comes around 5 MIU 8-hourly (1 mg colistimethate sodium = 12,500 IU of colistin).[3] Favorable clinical outcome could be achieved in patients with VAP due to carbapenemase producing

Fig. 1: Ventilatory circuit with nebulizer chamber attached

Pseudomonas aeruginosa and *Acinetobacter baumannii*, using this aerosolized colistin alone, at the dose and aerosolization technique used in our study.[9] Thirdly, we used a vibrating mesh nebulizer for colistin aerosolization. With finer droplet generation and minimal residual volume, these nebulizers achieve superior aerosol delivery compared to jet nebulizers.[12,13] Ultrasonic nebulizers have a risk of denaturing polypeptides due to heat generation.[6] Fourthly, we used specific ventilator setting during aerosol delivery to promote laminar flow during aerosolization with better distal lung delivery of drugs.[6] Finally, we used a specifically designed ventilator circuit (NebHME Circuit, PneumoCare, New Delhi, Fig. 1) to ensure minimal loss of colistin in the circuit.[14] The circuit had a provision to place a nebulizer 20 cm from the Y-piece in the inspiratory limb and a smooth inner surface of the inspiratory limb between the nebulizer attachment to Y-piece to minimize turbulence.

Conclusion

Treatment of HAP due to XDR gram-negative pathogens with high-dose colistin aerosolization, delivered with a specific strategy, in addition to systemic polymyxin-B showed a strong but nonsignificant trend towards better outcomes in all clinical end-points without any increase in adverse effects.

Ethical Approval

The study was approved by Institutional Ethics Committee reference no EC/2021/27 dated 07-07-2021.

Acknowledgments

The authors acknowledge contributions of all staff members of our unit for participating in the clinical management of all ICU patients during the study period.

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Supplementary Material

All the supplementary materials are available online on the website of www.IJCCM.org

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