Section: Anaesthesiology

Original Research Article

TREATMENT OF MULTI DRUG RESISTANT GRAM NEGATIVE BACILLI WITH INHALED POLYMYXIN

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Abstract

Background: The present study was conducted to assess the safety and efficacy of aerosolized polymyxinb in comparison to intravenous polymyxinb therapy for treatment of MDR GNB (Multidrug resistance gram negative bacteria). **Materials and Methods:** Study was conducted in the ICU of Osmania General Hospital, Hyderabad over a period of one year. **Result:** Aerosolized polymyxin B was safe than the intravenous polymyxinb therapy for treatment of MDR GNB. **Conclusion:** Aerosolized administration of Polymyxin B is a promising therapy for management of patients with pneumonia due to multi drug resistant Gram-negative bacteria.

INTRODUCTION

Emergence of nosocomial bacterial pathogens with acquired resistance to almost all available antimicrobial agents, namely 'superbugs', has severely threatened therapeutic choices in the last decade.[1] A major challenge has arisen regarding the treatment of infections caused by Gram-negative bacilli, particularly those with high level intrinsic resistance to many antibiotic classes and extreme ability to acquire resistance, such as Pseudomonas aeruginosa and acinetobacterbaumannii.[2] No new antibiotic is there even in the drug development pipeline for MDR Gram-Negative bacteria.[3]

The clinical and economic consequences of the emergence of multidrug-resistant Gram negative bacteria in the intensive care unit (ICU) setting, combined with the high mortality rate among patients with nosocomial pneumonia, have stimulated a search for alternative therapeutic options to treat such infections.[4]This therapeutic void has created a resurgence of interest in polymyxins. Because of nephrotoxicity, neuromuscular blockade, neurotoxicity with systemic use of polymyxins, aerosolized therapy is used as an alternative method for treating MDR GNB.[5]

Aerosolized therapy in place of systemic treatment appears promising, but the current published data are too limited to allow determination of the incremental benefit of aerosolized treatment to Systemic treatment.[6]

The aim of the study is to compare the following factors in two groups:

A) Group A treated with nebulized polymyxin-B.
B) Group B treated with intravenous Polymyxin-B.

1. Outcome at end of treatment:
A) Improvement
B) Cure
C) Failure
2. Fever response to therapy
3. Adverse effects to therapy

MATERIALS AND METHODS

Study was conducted in the ICU of Osmania General Hospital, Hyderabad which is a tertiary care centre. Study was performed over a period of one year. The study protocol was approved by ethical committee of the institution. Informed consent from the patient's kin was taken.

Inclusion Criteria

- Cases of either sex aged between 18 - 70 years.
- Patients on ventilator for >48 hours.

Exclusion Criteria

- Patients with pneumonia prior to ICU admission
- Patients with ARDS(Acute respiratory distress syndrome)
- Patients having pulmonary edema
- Patients with raised renal parameters

Inclusion & exclusion criteria were choosen to prevent variables identified to be associated with mortality in mechanically ventilated patients.

Study design: A Comparative two group randomized clinical study with 50 patients with 25

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patients in Group A and 25 patients in group b over one year period (August 2011 through July 2012) with pneumonia caused by MDR-GNB were treated with nebulized polymyxin – B. Compared with I.V Polymyxin –B in equal number of patients. It is undertaken to study the outcome of therapy, fever response to therapy and side effects.

The patients were divided randomly into two groups: Group – A: Polymyxin - B inhaled for 14 days 2 mg/kg/day in two divided doses in a solution of 5 ml of distilled water through a conventional nebulizer. Approximately 20 min before the polymyxin B inhalation, an aerosolized beta2-agonist was administered. Group – B: Polymyxin – B i.v for 14 days 2 mg/kg/day in two divided doses administered over one hour.

Data Collection: The following information was obtained for each patient: Age, Gender, Diagnosis, Duration of ICU stay, Duration of MV (Mechanical ventilation),Fever response to therapy, Adverse effects during therapy, Outcome at the end of treatment.

Criteria for pneumonia caused by MDR-GNB: 48 hrs after intubationX – ray showing new or progressive pulmonary infiltrates, Fever> 100.4 º F, Increased amount and purulence of tracheal secretions, Leucocytosis> 12,000 cells/mm3 .If resistant to 4 or more of the following antimicrobial agents: Piperacillin–tazobactam, Ceftazidime ,Cefoperazone, Ciprofloxacin, Imipenem, Gentamycin , Amikacin

An endotracheal aspirate was obtained immediately following clinical suspicion. Microbiological diagnosis of VAP was established by positive cultures of bronchial secretions with isolation of an MDR gram-negative bacterium with a concentration of ≥104 CFU/ml.

The response to treatment was assessed at the time of discharge from the ICU or at the end of antimicrobial therapy, especially if the patient remained hospitalized for a non VAP-related disease.

The primary end point of the study was the clinical outcome of VAP. In patients with normal renal function, nephrotoxicity was defined as a serum creatinine value >2 mg/dl. Bronchospasm during inhaled polymyxin, defined as the increase of respiratory frequency associated with wheezing, was evaluated.

The therapeutic response was evaluated by one of the following criteria: Improvement. Defined as the reduction and improvement of the appearance of tracheal secretions, reduction ordisappearance of chest X-ray alterations, normalization of leukocyte count, patient becoming afebrile and improvement of the mechanical ventilation parameters (FIO2 and positive end expiratory pressure [PEEP]).Cure. Criteria for improvement plus disappearance off ever, return of spontaneous ventilation, and discharge from the ICU or the hospital. Failure. All the situations not classified as improvement or cure.(persistence or worsening of presenting symptoms and/or signs of infection during polymyxin administration).

The patients were included if they met the inclusion criteria and the criteria for pneumonia described elsewhere(Garner et al., 1988) caused by MDR-GNB. Tracheal secretions were obtained through tracheobronchial suction in patients submitted to intubation or tracheostomy and a growth of >/=104 CFU/ml was considered significant.

Statistical Methods: Descriptive statistical has been carried out in the present study. Results on continuous measurements are presented on mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data are made, Assumption: 1.) Dependent variables should be normally distributed, 2.) Samples drawn from the population should be random, Cases of the samples should be independent.

Statistical analysis was done by applying Chi-square test and students ‘t’ test to analyse the data, p value was determined. P > 0.05 is not significant, P< 0.05 is significant, P< 0.001 is highly significant.

RESULTS

The patients who took part in this study were in the age group of 18 to 70 years.The study showed overall age incidence is found maximum in the age group 31-50 years with 48% (12 cases in group-A) 52%(13 cases in Group-B)and second common age group is 18-30 years with 28% (7 cases in group-A) 24%(6 cases in Group-b) followed by 51-70 years with 24%(6 cases in group-a) 24%(6 cases in Group-b) were explained in [Table 1].

The T-value is 0. The P-Value is 1. The result is not significant at p < 0.05.On statistical comparison the two groups were comparable.

On statistical analysis samples are gender matched with P = 1.000

The study was undertaken in 17 male patients in group-A,8 male patients in group-B,and 17 female patients in group-A,8 female patients in group-B [Table 2].

Table 1: Age Distribution of Patients Studied

Age in yrs	GROUP-A	%	GROUP-B	%
18-30	7	28	6	24
31-50	12	48	13	52
51-70	6	24	6	24
Mean age in years (±SD)	41.4±13.10		41.36±13.06	

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Table 2: Gender Distribution of Patients

Gender	Group-A	Group-B
Male	17	8
Female	17	8

Table 3: Duration of ICU Stay

	Group-A	Group-B
Mean duration of stay	28.68±9.15	31.64±9.16

Table 4: Microorganism Isolated

Microorganism	Group-A		Group-B	
Pseudomonas aeruginosa	15	60%	14	56%
Acinetobacterbaumannii	5	20%	4	16%
Klebsiella pneumonia	5	20%	7	28%

Table 5: Outcome of Therapy

Outcome	Group-A		Group-B	
Improvement	11	44%	10	40%
Cure	11	44%	5	20%
Failure	3	12%	10	40%

Mean duration of stay in group A(28.68±9.15) and group B (31.64±9.16) [Table 3].

The T-value is 1.142809. The P-Value is 0.258786. The result is not significant at $p < 0.05$.

Pseudomonas aeruginosa in group A-15, Group b-14, acinetobacterbaumannii in group A-5, Group B-4, klebsiellapneumonia in Group A-5, Group B-7 [Table 4]

The chi-square statistic is 0.4789. The P-Value is 0.78705. The result is not significant at $p < 0.05$.

Improvement in group A-11, Group B-10, cure in Group A-11, Group B-5, failure in Group A-3, Group B-10 [Table5]

The chi-square statistic is 6.0668. The P-Value is 0.04815. The result is significant at $p < 0.05$.

DISCUSSION

Inhaled antibiotics have been used based on the rationale that the drug would concentrate at the infection site minimizing toxicity of systemic administration, and this strategy has gained strength. Gram-negative bacilli and especially P. Aeruginosa are among the important causes of nosocomial infections worldwide. In this setting, treatment with inhaled polymyxin B may prove to be an interesting alternative because the systemic use of polymyxins seems to yield poor results.

There are no other studies which compare inhaled polymyxin B alone with iv polymyxin B alone. The present study was performed to evaluate the effectiveness and safety of inhale dpolymyxin B in MDR pneumonia patients.

In this study the inhalational and intravenous dosing regimen was selected based on previous animal studies and ICU practices in this institution.

In this study Group-A received 2mg/kg(20000U/kg) polymyxin B via inhalation and Group-B received 2mg/kg polymyxin B intravenously. These doses were given in two divided doses as preferential accumulation of polymyxin B in the kidneys is a non-passive process and q12h dosing was less nephrotoxic than q6h dosing.[9]

In this study improvement, cure and failure rates were 44%,44% and 12% respectively in Group-A(inhaled polymyxin b)while improvement, cure and failure rates were 40%,20% and 40% in group-B(iv Polymyxin B) which was statistically significant. GraziellaH.Pereiraa et al study showed that the outcome of treatment with inhaled polymyxin B was cure in 53%, improvement in 42% and failure in 5%.

In our study fever response to study was better in Group-A (inhaled polymyxin B) which was statistically significant. There are no studies which compared this factor.

In our study adverse events to polymyxin B inhalation (bronchospasm) occurred in 16% of the patients in group-A but did not lead to suspension of treatment. Pereiraa et al,[8] in their study showed that adverse events during polymyxin B inhalation occurred in 21%. Nephrotoxicity occurred in 28% of Group-B patients while there was no nephrotoxicity in Group-A patients. . Neurotoxicity, while difficult to assess in severely ill ICU patients, appeared minimal.

In the ICU setting, sepsis, hypotension and the use of other nephrotoxic drugs contribute to impairment of renal function. Our study was not able to exclude the confounding impact of these variables because of our reliance on sometimes incomplete medical records and the complex nature of treating patients in ICU.

Mean duration of ICU stay was 28.68±9.15 days in Group-A, while it was 31.64±9.16 days in Group-B. This was not statistically significant with p-value 0.258786. Kofteridiset al in their study also showed that ICU stay in two groups was not statistically significant.

Mortality rates (VAP mortality and all-cause mortality rates) were not compared in our study because we excluded patients with raised renal parameters, ARDS and pulmonary edema. This

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would have been confounding factor in evaluation of mortality rates.

Duration of mechanical ventilation was also not evaluated as the patients were being ventilated mechanically for reasons other than MDR VAP.

Though there are limitations in our study outcome of inhaled polymyxin B therapy is significant. The response was good and might be explained by the possible high concentration of the inhaled drug in the pulmonary compartment.

In our study the isolates were not tested for polymyxin B resistance because microdilution was not available and disk diffusion is not a reliable method.[10]This could have acted as a confounding factor in failure cases.

The pharmacokinetic properties and dosing strategies of aerosolized polymyxin are not well defined. Whether the various forms of polymyxin used for inhalation therapy or the different types of nebulizing systems influence the effectiveness and safety of colistin remains to be determined.[11-14]

Further pharmacokinetic-pharmacodynamic studies in which serum concentrations achieved by varying doses of polymyxin are compared to the MIC of the infecting organisms are required so that the optimal dose of polymyxin can be determined. This is important not only for optimal effectiveness of the drug but also to prevent polymyxin resistance.

CONCLUSION

Inhaled Polymyxin – B deposits the drug at the site of infection and facilitates better antimicrobial action inhaled polymyxin B was useful in treatment of nosocomial pneumonia caused by MDR-GNB in mechanically ventilated patients. As the drug is given by inhalational route systemic side effects can be minimized. The results of this study should lead to randomized controlled studies to establish the role of this form of treatment.

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