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Comparison of Cefoperazone + Sulbactam Versus Polymyxin B in the Management of Ventilator Associated Pneumonias Caused by Multi-Drug Resistant Acinetobacter

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A B S T R A C T

The present study entails a comparative analysis of the efficacy of polymyxin B and cefoperazone with sulbactam in the treatment of pneumonias induced by multidrug-resistant Acinetobacter strains. In the experimental group, the gender distribution was exactly the same (males: 21; females: 15). More co-morbidities exist in Group-II than in Group-I. In groups I and II, the mean ICU stays were respectively 11.86 days plus 2.06 SD and 11.47 days plus 1.61 SD. Day 2 post-therapy saw group mean CPIS at 7.781.48 and group-II at 7.081.23, respectively. The clinical response was seen in group-I (n=11/36) and group-II (n=24/36) patients in accordance with our operational criteria. Similar mortality rates applied to both groups. In line with our hypothesis, 31% (n=9/29) of group I survivors and 65.6% (n=21/32) of group II survivors both showed effectiveness (p=0.007).

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a type of pneumonia that occurs in people who have been subjected to mechanical ventilation for a minimum of 48 hours. This condition is commonly acquired within healthcare settings [5]. VAP continues to be the second most prevalent cause of mortality in patients with nosocomial infections. The incidence of VAP exhibits considerable variation, ranging from 5% to 60%, with an average occurrence of approximately 10%. Moreover, the overall rate of VAP surpasses 13 cases per 1000 ventilator days [22, 8]. It is noteworthy that VAP has a significant mortality rate inside critical care units, ranging from 20% to over 50% . In European countries, the average mortality rate for early VAP stands at approximately 20%, whereas late VAP surpasses 30% . In the United States, the mortality rate for VAP is reported to be 13%. [8].

The use of various preventive measures, such as reducing the duration of mechanical ventilation and advocating for early extubation, has resulted in a sustained decline in mortality rates over the course of several years. Nevertheless, the task of selecting the proper antibiotics for the treatment of VAP continues to pose a significant problem. Based on certain estimations, it has been observed that roughly 50% of antibiotics provided to patients within the critical care unit are specifically intended for the treatment of VAP) . Given the significant impact of antibiotic therapy selection on disease outcomes and the high rate of initial empirical therapy ineffectiveness in up to 70% of cases [1], it is imperative to priorities the development of innovative treatment strategies and the optimization of existing treatments for VAP.

Because of the increase of MDR Acinetobacter strains, VAP is a common nosocomial infection in critically sick patients, and its management can be challenging. Two commonly used medications for the treatment of Acinetobacter infections that are resistant to several antibiotics are cefoperazone-sulbactam and polymyxin B. However, there is limited data available when comparing the effectiveness and safety of these two antibiotics in the treatment of VAP brought on by MDR Acinetobacter.

The effectiveness of cefoperazone-sulbactam and polymyxin B in treating MDR Acinetobacter infections has been evaluated in a number of studies. In critically ill patients with Acinetobacter bacteremia, Langley et al. examined the effects of cefoperazone-sulbactam and polymyxin B. They found that cefoperazone-sulbactam was associated with a lower death rate and a shorter hospital stay. Comparably, Zhang et al. discovered in a meta-analysis that cefoperazone-sulbactam had a higher clinical cure rate and a lower death rate than polymyxin B when treating MDR Acinetobacter infections [3]. The effectiveness and safety of these antibiotics in treating VAP caused by MDR Acinetobacter need more investigation, as there is insufficient data to compare cefoperazone-sulbactam with polymyxin B. This study set out to find out how well cefoperazone-sulbactam and polymyxin B worked together to treat VAP brought on by MDR Acinetobacter strains. The evaluation of the clinical cure rate was the study's main objective, with supplementary considerations. Result such as the death rate, length of hospital stay, and frequency of unfavorable events.

METHODOLOGY

In the Medical Intensive Care Unit (MICU) of the Department of Critical Care Medicine at the Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, a one-year randomized controlled trial was carried out. Comparing randomized control trials to conventional studies reveals additional advantages in study design. For every study group, a total of 36 cases will be enrolled. 72 patients with ventilator-associated pneumonias caused by multidrug-resistant Acinetobacter will make up the study sample in its whole. To determine the sample size, the non-probability sampling technique was employed.

Every patient in succession had pneumonias related to ventilators and caused by Acinetobacter multidrug resistant. The study design would not include the following patients. people with a history of pneumonia and those with a known allergy to polymyxin B or Cefoperazone + Sulbactam. Patients with concurrent infections at other sites and those with VAP due to Acinetobacter resistant to either Cefoperazone + Sulbactam or polymyxin B. Consent was requested from those who acquired VAP 48 hours after being admitted to the MICU and were shown to have multidrug resistance in microbiology. At the time of enrollment, patients or caregivers provided written informed permission.

Randomization was used to assign the patients to either Polymyxin B (group II) or Sulbactam + Cefoperazone (group I). Every patient received a dose that was precisely calculated based on their body weight in accordance with the prescribed standard drug schedule. For exact dosage calculations, we used "Medscape." Following the seventh day of treatment, the primary research outcome (drug efficacy) was assessed using the Procalcitonin level and CPIS in accordance with established recommendations (Infectious Disease Society of America and American Thoracic Society, 2016).

RESEARCH RESULT

In the present clinical trial, we have included a total of seventy-two (n=72) consecutive patients with ventilator associated pneumonias caused by multi drug resistant Acinetobacter. Gender distribution was similar in both groups. In group I there were 50.0% (n=18/36) males and 50.0% (n=18/36) females and in group II there were 58.3% (n=21/36) males and 41.7% (n=15/36) females (P=0.478). Mean age was 44.1 years ± 19.4 SD in group I patients and it was 40.4 years ± 17.3 SD in group II patients (P=0.412). In group I there were 41.7% (n=15/36) patients had DM, 19.4% (n=7/36) had HTN, 13.9% (n=5/36) had CVD, 19.4% (n=7/36) had kidney disease and 5.6% (n=2/36) had liver disease. The percentages were 47.2% (n=17/36), 16.7% (n=6/36), 16.7% (n=6/36), 11.1% (n=4/36) and 8.3% (n=3/36) respectively in group II (P=0.860). In group I patients mean length of ICU stay was 11.86 days ± 2.06 SD and it was 11.47 days ± 1.61 SD in group II patients (p=0.375, Table 01).

Randomization was used to assign the patients to either Polymyxin B (group II) or Sulbactam + Cefoperazone (group I). All patients were monitored until their ICU release, until they passed away while in the ICU, and until day 7, when the CPIS and procalcitonin levels in the two groups were compared for those who did not pass away. Following the seventh day of treatment, the primary study outcome (drug efficacy) was assessed using CPIS and Procalcitonin levels in accordance with established protocols. The effectiveness of the medication was determined by measuring the clinical response to therapy in the first two days by reducing the CPIS by at least two points, or by day five by CPIS being less than five, PCT Value 0.25 to 0.5 ng/mL, or a drop of 80% (Table 02).

Table 1**:** Patient demographic with co-morbidities

Gender	**Sulbactam+Cefoperazone**	**Polymoxin B**	**Total**	**P-Value**
Male	18 (50.0%)	21 (58.30%)	39(54.20%)	0.478
Female	18 (50.0%)	15 (41.70%)	33 (45.80%)	
Total	36 (100.0%)	36 (100.0%)	72 (100.0%)	
Mean age (in Years)	44.1	40.4	.	0.412
Base Line comorbidities				
DM	15(41.7%)	17(47.2%)	32(44.4%)	0.86
HTN	7(19.4%)	6(16.7%)	13(18.1%)	
CVD	5(13.9%)	6(16.7%)	11(15.3%)	
Kidney Disease	7(19.4%)	4(11.1%)	11(15.3%)	
Liver Disease	2(5.6%)	3(8.3%)	5(6.9%)	
Total	36(100%)	36(100%)	72(100%)	
Stay in ICU (in Days)	11.86	1147.00%		0.375

Table 2: Mean CPIS, Procalcitonin and Clinical outcomes.

Time	**Groups**	**Mean CPIS**	**SD**	**P-value**
Day 0	SULBACTAM + CEFOPERAZONE	8.31	0.89	0.789
	POLYMOXIN B	8.36	0.87	
Day 2	SULBACTAM + CEFOPERAZONE	7.78	1.48	0.033
	POLYMOXIN B	7.08	1.23	
Day 5	SULBACTAM + CEFOPERAZONE	6.56	2.17	0.005
	POLYMOXIN B	5.06	2.2	
Procalcitonin		**Mean procalcitonin ng/ml**	**SD**	**P-Value**
Day 0	SULBACTAM +	0.638	0.033	0.183

	CEFOPERAZONE			
	POLYMOXIN B	0.648	0.032	
Day 7	SULBACTAM + CEFOPERAZONE	0.554	0.129	0.011
	POLYMOXIN B	0.464	0.165	
Clinical Response	**Present**	**Absent**	**Total**	**P-Value**
Day 2				
SULBACTAM + CEFOPERAZONE	8(22.2%)	28(77.8%)	36(100%)	0.026
POLYMOXIN B	17(47.2%)	19(52.8%)	36(100%)	
Day 5				
SULBACTAM + CEFOPERAZONE	11(30.6%)	25(69.4%)		0.002
POLYMOXIN B	24(66.7%)	12(33.3%)		
Mortality	**Alive**	**Dead**	**Total**	**P-Value**
SULBACTAM + CEFOPERAZONE	32(88.9%)	4(11.4%)	36(100%)	0.326
POLYMOXIN B	29(80.6%)	7(19.4%)	36(100%)	
Efficacy	**Present**	**Absent**	**Total**	**P-Value**
SULBACTAM + CEFOPERAZONE	9(31.0%)	20(69.0%)	29(100%)	0.007
POLYMOXIN B	21(65.6%	11(34.4%)	32(100%)	

DISCUSSION

VAP in critically ill patients is often associated with the multidrug-resistant gram-negative bacteria Acinetobacter baumannii. Patients with VAP frequently worsen in the intensive care unit (ICU) and acquire A. baumannii bacteremia, a condition that has negative consequences. The results of our study showed that 22.2% of patients in group I and 47.2% of patients in group II had a clinical response by the second day of treatment. Thirty-six percent of patients in group I and sixty-seven percent of patients in group II showed signs of a clinical response by the fifth day after therapy started. Our investigation shows results that are rather consistent with the body of current literature on treatment outcomes.

Remarkably, in recent times, polymyxins have emerged as one of the few families of drugs that may effectively treat infections caused by gram-negative bacteria that are resistant to drugs, including Enterobacteriaceae, Pseudomonas aeruginosa, and A. baumannii. Since polymyxins are toxic, it is unknown what combination of antibiotics or therapeutic dose will work best [4]. There aren't many research looking at polymyxin user profiles and trying to figure out the optimal dosage. Our findings align with previously published research in this domain. For instance, Brotfain and colleagues conducted a study wherein they meticulously examined the clinical and laboratory records of 129 intensive care unit (ICU) patients afflicted with ventilator-associated pneumonia (VAP) caused by multidrug-resistant Acinetobacter baumannii. Among these patients, 46 (35%) had simultaneous MDR A. baumannii bacteremia. Notably, their investigation revealed a higher ICU mortality rate among patients with VAP accompanied by A. baumannii bacteremia as opposed to those who did not exhibit bacteremia. The overall study mortality was 15.3%; the discrepancy is probably because the recruited patients' clinical state varied in the published studies.

In order to assess the efficacy and safety of intravenous polymyxin B in patients with multidrug-resistant Gram-negative bacterial infections, Falagas ME et al. reviewed the available literature. The overall mortality and nephrotoxicity in individuals receiving either combination or monotherapy of intravenous polymyxin B [11]. They incorporated 43 research about the safety and/or efficacy of intravenous polymyxin B; they showed no discernible variation in the safety and efficacy of intravenous polymyxin B administered as combination therapy or as monotherapy. According to Khan et al., there is a direct correlation between the duration of hospital stay and treatment outcomes, including infections. Given that carbapenem-resistant microbes are common in various regions of the country, the local microbiota profile in many Brazilian hospitals, particularly tertiary care facilities, justifies the empirical prescription of polymyxins . Not only are polymyxins harmful, but the widespread empirical use of this family of drugs puts pressure on antimicrobial selection, which is concerning. Although Bento et al. examined the use of polymyxins for the treatment of VAP at a hospital where carbapenem-resistant gram-negative bacteria were common, there have been few epidemiological studies of the use of polymyxins

The etiological agent of VAP was identified as A. baumannii in 121 instances; the fatality rate was substantially greater than in the current investigation, however this was likely due to variations in the patients' clinical status.

In conclusion, the theme that emerged from our study and the extensive literature analysis on the topic is that polymyxins are now among the few medication classes that are successful in treating infections caused by gram-negative bacteria that are resistant to several drugs, including A. baumannii and other similar bacteria.

CONCLUSIONS

In the context of clinical response and therapeutic effectiveness, individuals administered Polymyxin B exhibited superior outcomes compared to those receiving Sulbactam and Cefoperazone. Although the Polymyxin B-treated group demonstrated a higher mortality rate, this discrepancy in mortality rates between patients treated with Polymyxin B and those treated with Sulbactam and Cefoperazone did not attain statistical significance.

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