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ORIGINAL ARTICLE

Cerebrospinal Fluid Sterilization with Intrathecal Polymyxin in Addition to Parenteral Polymyxin in Nosocomial Acinetobacter Meningitis

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ABSTRACT

Background: For the last few decades there has been a substantial concern regarding the increasing prevalence of multidrug resistant (MDR) *Acinetobacter species* in hospitals.
Aim: To determine the outcomes with intrathecal polymyxins therapy in patients with multidrug resistant *Acinetobacter species* nosocomial meningitis.
Place and duration of study: This Retrospective study was conducted in the Department of Infectious Diseases, Aga Khan University Hospital, Karachi Pakistan between 2010 and 2014.
Methodology: Twenty six patients who developed post neurosurgical MDR *Acinetobacter* nosocomial meningitis age above 18 were included, while those with polymicrobial meningitis, and those patients who only received intravenous polymyxins were excluded. The primary outcome is ability and time to sterilize the cerebrospinal fluid
Results: The mean age was 42.9±11.5 years. Cerebrospinal fluid sterilization was observed in 24 patients in a median of 4 days. One patient made complete recovery, 16 patients recovered with neurological deficits and five patients expired. A trend of early cerebrospinal fluid sterilization was observed in patients with continuous intrathecal therapy. The time to cerebrospinal fluid sterilization is similar with intrathecal colistin or polymyxin.
Conclusion: Intrathecal polymyxins are safe and efficacious in the treatment of multidrug resistant nosocomial *Acinetobacter species* meningitis.
Keywords: Intrathecal, Polymyxins, Multidrug resistant, *Acinetobacter species*, Nosocomial, Meningitis

INTRODUCTION

Acinetobacter species is an increasingly important nosocomial pathogen with outbreaks reported in almost every continent within the past decade.[1,2] For the last few decades there has been a substantial concern regarding the increasing prevalence of multidrug resistant *Acinetobacter species* in hospitals. Due to its impressive collection of resources for resistant mechanisms, it is resistant to almost all available antibiotics, leading to a re-introduction of polymyxins in the treatment of this organism.[3-5]

While *Acinetobacter species* usually causes ventilator acquired pneumonia, blood stream infections and wound infections, nosocomial meningitis has also been reported.[2] However studies have demonstrated a very low level of polymyxin penetration into the cerebrospinal fluid (CSF) following intravenous (IV) administration.[6,7] Therefore, intrathecal (IT) administration may have an effective role in the treatment of meningitis due to multidrug resistant *Acinetobacter species.*[8-13] While case reports and case series have shown potential benefit of the addition of intrathecal polymyxins to parenteral polymyxins, there is very limited data on intrathecal polymyxin therapy for multidrug resistant *Acinetobacter species* meningitis.[1]

The objective of the study was to determine the outcomes with intrathecal polymyxins therapy in patients with multidrug resistant *Acinetobacter species* nosocomial meningitis.

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MATERIALS AND METHODS

This retrospective study was conducted at Department of Infectious Diseases, Aga Khan University Hospital, Karachi Pakistan between 2010 and 2014. Twenty six patients who developed post neurosurgical MDR *Acinetobacter* nosocomial meningitis age above 18 were included. Patients with polymicrobial meningitis and those who received intravenous polymyxins only were excluded. Nosocomial meningitis was defined based on Center for Disease Control's definition for meningitis as an infection occurring after a neurosurgical procedure with *Acinetobacter species* cultured from cerebrospinal fluid (CSF) and the presence of one of the following: fever (>38°C), headache, signs of meningeal irritation and raised serum leukocyte count.

The files of patients with positive CSF cultures with MDR *Acinetobacter species* were reviewed by the primary investigator. Data was recorded on a Performa that included demographic data, therapeutic parameters, and outcomes (median days to CSF sterilization). CSF examination was repeated 48 hours after initiation of intrathecal polymyxin therapy. Subsequent CSF examination was done according to the clinical condition of the patient. CSF sterilization was defined as negative CSF culture at any point after initiation of intrathecal polymyxins therapy. Cerebrospinal fluid time to sterilization was defined as when CSF becomes sterile after initiation of intrathecal polymyxins therapy. Simplified Acute Physiology Score (SAPS) II calculator to predict hospital mortality was used to assess the mortality on admission as well as at time of onset of nosocomial meningitis.[14]

Continuous variables with normal distribution were summarized as means with standard deviations. Variables with skewed distribution were summarized as medians with inter-quartile ranges (IRQs). Categorical variables were presented as proportions (percentages). Mann Whitney U test for used to compare continuous variables with skewed distributions. All analyses were conducted using the Statistical package for social science SPSS-20. All p-values were two sided and considered as statistically significant if <0.05.

RESULTS

There were 24 males and 2 females with mean age was 42.9±11.5 years. Most of the patients did not have any co-morbid conditions 62.9% while 6 (23.1%) patients were hypertensive and 2 (7.7%) were diabetic. The most common reason for neurosurgical procedure was trauma complicated with subdural hematoma or hydrocephalus 11 (42.3%) patients followed by vascular diseases 8 (30.6%) patients and neoplasms 7 (26.9%) patients. Consequently, foreign bodies were inserted at the time of neurosurgical procedure in 19 patients (73.1%), of which extra-ventricular drains (EVD) were inserted in 12 (46.2%) while the 6 (23.1%) had external lumbar drains and 1 (3.8%) had aventriculo-peritoneal shunt. The median time from procedure to development of meningitis was 7 days (range 4-9 days). The SAPS estimated mortality at the time of onset of meningitis was higher with mean 27.2±24 than at the time of admission (18.89±25.7) [Tables 1-2].

While all the patients received intrathecal therapy within 48 hours of onset of meningitis, a variety of treatment regimens were used. Given the lack of availability of colistin, most patients (17 of 26) received therapy with polymyxin B. Polymyxin B was given at a dose of 750,000 IU twice per day intravenously with 50000 IU intrathecal. Similarly, Colistin was used at 300,000 IU every 8 hourly (after loading dose of 900,000 IU) with 300,000 IU intrathecal. Most patients 20 (74%) were given intrathecal therapy daily while alternate day therapy was used in the rest. Adjunctive parenteral meropenem (2g every 8 hours) was also used in most patients 22 (84%) [Table 1].

Cerebrospinal fluid sterilization was observed in 24 patients in a median of 4 days (2-6). The median time to CSF sterilization in carbapenem combination therapy was similar to if carbapenems were not used (4.5 days vs. 2 days; p-valve 0.22). Additionally, outcomes were similar with intrathecal polymyxin vs intrathecal colistin4 days vs. 4.53 days, p-valve 0.43). In the daily intrathecal colistin/ polymyxin therapy the time to CSF sterilization was 4 days while in intermittent continuous intrathecal colistin/ polymyxin therapy the time to CSF sterilization was 2 days (p valve 0.22).

The patients who failed CSF sterilization died within 24 hours of intrathecal therapy. There is no significant difference between intrathecal polymyxin and colistin in terms of CSF sterilization. Only five (19.2%) patients developed acute renal failure with polymyxin therapy. The 30 days mortality was 19.2% (5 patients) five patients expired; whereas 16 patients recovered with CNS deficits and only one patient achieved complete recovery. The main of cause of death was myocardial infarction in three patients while one died of massive pulmonary embolism and other because of sepsis. All of these expired within 14 days of development of meningitis.

Table 1: Characteristics of the patients n=26

Variable	No.	%
Gender		
Male	24	92.3
Female	2	7.7
Age (years)	42.9±11.5	
Co-morbidity		
Hypertension	6	23.1
Diabetes	2	7.7
No co-morbidity	18	69.2
Primary diagnosis		
Aneurysm	5	19.2
Head RTA injury	4	15.4
Gunshot head injury	4	15.4
Craniopharyngioma	3	11.5
Cerebellar infarct	2	7.6
Basal ganglia bleed	1	3.8
Cervical gunshot injury	1	3.8
Dorsal cord lipoma	1	3.8
Fracture of skull base	1	3.8
Oligoastrocytoma	1	3.8
Oliogodendroglioma	1	3.8
Haemangioblastoma	1	3.8
Spinal stenosis	1	3.8
Neurosurgical procedure		
Decompression craniotomy	14	53.8
Excision of space occupying lesion	6	23.1
Burr hole surgery	2	7.7
Aneurysm coiling	1	1.4
Other	3	11.5
Intrathecal polymyxin/colistin		
Colistin	11	42.3
Polymyxin	15	57.6
Foreign body		
Yes	19	73.1
No	7	26.9
Intrathecal polymyxin/colistin frequency		
Alternate day	7	26.9
Daily	19	73.1
Adjuvant parenteral meropenem		
Yes	22	84.6
No	4	15.4

Table 2: Type of foreign body and removal (n=19)

Variable	No.	%
Type of foreign body		
External ventricular drain	12	63.1
External lumber drain	6	31.5
Vertriculoperitoneal shunt	1	5.4
Removal of foreign body		
Yes	5	26.3
No	14	73.7

DISCUSSION

We report 26 patients with nosocomial *Acinetobacter species* meningitis in which intrathecal polymyxin/colistin used in combination with parenteral polymyxin/colistin. We have previously reported our results with combination treatment with intrathecal and intravenous antibiotics for post-operative meningitis.[15] In both these studies, we found the combination to be both safe and efficacious in sterilizing the CSF, despite late removal of hardware. However, despite sterilization and low mortality; long term sequalae occurred frequently, though it is unclear if this was due to the meningitis or the primary pathology.

Treatment of multidrug resistant *Acinetobacter species* meningitis is problematic and no clear guidelines have been established due to the paucity of information. Given the lack of CSF penetration of the polymyxins, the addition of intrathecal polymyxins is recommended. In a prospective case control randomized study by Ziaka et al[12], the combination of intraventricular and intravenous colistin resulted in higher CSF concentration as compared to intravenous colistin alone in patients with multidrug resistant gram negative bacteria EVD ventriculitis. In our study of *Acinetobacter species* meningitis, CSF sterilization was achieved in almost all patients in a median time of 4 days. This is in line with other studies which have also reported a median CSF sterilization time between 2.5-15 days (1-82 days).[8,11,15-17]

However, there are several questions pertaining to the intrathecal administration of polymyxins which our case series helps address. Firstly, dosing is not well established and range from 120,000 IU to 500,000 IU.[10,12-16] Given the occasional detection of colistin resistant strains of *Acinetobacter species*, we opted for a higher dose of 50000 IU of polymyxin B or 300,000 IU of colistin intrathecally. Despite of higher doses no adverse effects were reported and intrathecal therapy was not discontinued in any patient due to side effects. Based on this and other reports, intrathecal polymyxin administration appears to be safe.[8-17] Given the lack of hardware, in some patients alternate dosing of polymyxins was used. This was appeared to be inferior to daily dosing and while did not reach statistical significance, patients on less frequent dosing trended towards poorer outcomes.

Our study had several limitations including the lack of a control arm and a small sample size. However, given the safety profile of intrathecal polymyxins and the high morbidity associated with *Acinetobacter species* meningitis, we do not feel a control arm could be justified.

CONCLUSION

Intrathecal colistin is safe and efficacious in the treatment of multidrug resistant nosocomial *Acinetobacter species* meningitis. Despite the lack of consensus on dosing, we recommend higher daily dosing to achieve sterilization.

Conflict of interest: Nil

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