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BRIEF REPORT

Polymyxin for the treatment of intracranial infections of extensively drug-resistant bacteria in children after neurosurgical operation

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Abstract

Background Increased meningitis caused by extensively drug-resistant bacillary presents a significant challenge in antibiotic selection. The aim of our study was to evaluate the efficacy and safety of polymyxin in the treatment of post-neurosurgical meningitis due to the extensively drug-resistant bacillary in children.

Methods We performed a retrospective study on post-neurosurgical meningitis caused by the extensively drug-resistant bacillary in children, who were treated with polymyxin for ≥ 3 days.

Results Among five post-neurosurgical meningitis cases that were included, the children were infected by *Acinetobacter baumannii* ($n=3$), *Klebsiella pneumonia* ($n=1$), and *Pseudomonas aeruginosa* ($n=1$). The drug susceptibility test showed that they were extensively drug-resistant bacillary. Two patients received intravenous polymyxin E. Three children received intravenous combined with intraventricular injection of polymyxin B. One patient infected by *Klebsiella pneumonia* eventually died of septic shock. No serious adverse effects of polymyxin were observed.

Conclusions Polymyxin is a safe and effective therapy for post-neurosurgical, multidrug-resistant bacillary meningitis in children.

Keywords Drug resistance · Meningitis · Neurosurgical procedures · Polymyxin

Introduction

Post-neurosurgical meningitis is a common complication, accounting for 0.8–7% of intracranial infections [1]. Meningitis caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) Gram-negative bacillary meningitis (GNBM) lead to a significant limitation in currently available treatment options. Due to the abuse of broad-spectrum antibiotics, the prevalence of meningitis with MDR/ XDR bacillary remains high. The percentage of meningitis following neurosurgery caused by *Acinetobacter baumannii* ranged from 15–21.74% [2],and the associated mortality rate was between 20 and 40% [3]. Due to increased resistance of MDR/XDR bacterial and lack of new antibiotics, the utilization of polymyxin have shown promising results [4]. The treatment strategies for XDR meningitis especially

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intraventricular injection of polymyxin have been used, but the effectiveness and adverse reactions of these treatments remain controversial [5].

Currently MDR/XDR bacteria are still susceptible to polymyxin. Polymyxin treatment for meningitis has been used in adults, but rarely in children, especially for intraventricular injections. We evaluated the therapeutic efficacy and safety of intravenous alone or combined with intraventricular therapy of polymyxin for post-neurosurgical XDR bacillary meningitis in children.

Methods

Patients

We conducted a retrospective study of post-neurosurgical XDR bacillary meningitis in children, who received polymyxin for ≥ 3 days. All patients were enrolled from June 2012 to May 2019 in the Surgical Intensive Care Unit (SICU) of a tertiary children's hospital. The meningitis caused by XDR of these patients was confirmed by Gram-negative bacillary cultures and drug sensitivity test from cerebrospinal fluid (CSF). The patients had no history of any infection before the neurosurgeries. The study was approved by the Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine (NO. 2020-IRB-012).

Strain culture and drug sensitivity test

VITEK2®Compact (Biomerieux, France) was used for drug susceptibility testing. MALDI-TOF (Time of Flight Mass Spectrometer, BRUKER, Germany) was used for strain identification. AST-GN16 drug sensitivity card was used to measure the minimum inhibitory concentration (MIC).

Results

Clinical manifestations and outcome

Five children with post-neurosurgical meningitis with positive cerebrospinal fluid (CSF) cultures who received polymyxin were reviewed, including infection with *Acinetobacter baumannii* ($n = 3$), *Klebsiella pneumonia* ($n = 1$), and *Pseudomonas aeruginosa* ($n = 1$). The male to female ratio was 2:3, the median age was 133 months (IQR 50.5 to 158.5 months).Three patients with craniocerebral trauma due to traffic accident, one patient with intracranial hemorrhage due to cerebral arteriovenous malformation, and another patient underwent craniocerebral surgery for neurofibromas. All patients had extraventricular drainage (EVD) tubes placed. All three children with traumatic brain injury had skull base fractures. The median length of time from first neurosurgery to CSF positive culture was 20 days (IQR 9 to 26.5 days). The median length of hospital stay was 71 days (IQR 31.5 to 81 days). The CSF showed an increased leukocyte (median 2780×10^6/L), and decreased glucose level (median 0.24 mmol/L). The level of protein content was increased (median 2728.8 mg/L) (Table 1).

Antimicrobial susceptibilities and treatment

The five cases received antibiotics to prevent perioperative infection before the diagnosis of intracranial infection. All cases received cefoperazone sulbactam. When the CSF culture was positive, antibiotics were actively adjusted based on the drug sensitivity results. The drug sensitivity test showed that all cases were infected with XDR pathogenic bacteria. Three cases were infected with *Acinetobacter baumannii* and one case with *Klebsiella pneumonia* that was susceptible to tigecycline and polymyxin. One case with *Pseudomonas aeruginosa* was susceptible to amikacin and polymyxin (Table 2). Two patients received polymyxin E. In addition, the other three received polymyxin B. These three patients also received intraventricular polymyxin B through the Ommaya reservoirs. Days to CSF culture turned negative in four surviving children was 21 days (IQR 12.8 to 25 days). One patient infected by *Klebsiella pneumonia* eventually died of septic shock and CSF culture was remained positive at death.

Follow-up

All four surviving children have been followed. One girl infected with *Pseudomonas aeruginosa* relapsed after 8 months. She developed an abscess behind the right ear, which subsequently caused a sinus track. The culture of pus of the abscess and CSF culture still showed *Pseudomonas aeruginosa*, which was still sensitive to polymyxin and amikacin. Polymyxin B was administered intravenously again for 60 days and intraventricular for 46 days. The child was cured of meningitis and transferred to a rehabilitation hospital. One case was in the vegetative state, and two children remained healthy and had normal hearing. Renal function was normal in all five children. No serious adverse effects of polymyxin were observed in our patients.

Discussion

Infections with XDR pathogens can lead to ineffective or delayed antibacterial treatment and are associated with poorer prognosis [6]. XDR pathogens have the highest mortality rates when the CNS is involved [7]. The incidence of post-neurosurgical meningitis caused by MDR or XDR

Table 1 Clinical manifestations and outcome

Case	Age (mon)	Gender	Primary diagnosis	Invasive procedure	Days from first neurosurgery to positive CSF culture	CSF routine			Highest renal function index during treatment		LHS (days)	*R*
						WBC (*106/L)	Glu (mmol/L)	Pro (mg/L)	BUN (mmol/L)	Cr (μmol/L)		
1	133	F	Arteriovenous malformation	Evacuation of hematoma/EVD	23	72	0.56	2728.8	2.77	28.0	72	N
2	14	M	Craniocerebral trauma	Craniotomy/EVD	7	2780	0.06	2641.7	3.98	26.0	36	N
3	87	F	Craniocerebral trauma	Craniotomy/EVD/Ommaya reservoirs	30	800	0.24	7499.0	2.68	35.1	71	N
4	161	M	Neurofibroma	Craniotomy/EVD/Ommaya reservoirs	11	5000	2.64	388.7	5.01	30.8	27	N
5	156	F	Craniocerebral trauma	Craniotomy/EVD/Ommaya reservoirs	20	7040	0.19	5771.0	2.72	37.6	90	Y

EVD external ventricular drain, *CSF* cerebrospinal fluid, *F* female, *M* male, *LHS* length of hospital stay, *R* relapse, *N* no, *Y* yes

bacillary has increased from 12 to 27% in all bacterial meningitis [8]. The guideline of the Infectious Diseases Society of America (IDSA) recommended that polymyxin could be administered intravenously or plus intraventricularly to treat meningitis caused by XDR [9], but the evidence in the guidelines is moderate. A meta-analysis showed no significant difference in mortality between polymyxin E and B treatment [10]. Polymyxin E and B have different pharmacokinetic characteristics. The antibacterial activity is slightly different between these two drugs, which may lead to differences in mortality and nephrotoxicity. In children, the recommended dosage of polymyxin E is 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg /kg IV q12h (maintenance dose).The recommended dosage of Polymyxin B is 2.5–3.0 mg/kg/d IV daily divided into 2 doses. The intraventricular injection dose for children is 0.5–2 mg/d for 3–5 days followed by every other day for 2–3 weeks. There are no guidelines for the treatment of polymyxin in children with post-neurosurgical meningitis.

In our study, cultures and drug sensitivity tests from CSF showed XDR to the tested antibiotics except for tigecycline and polymyxin. However, concentration of tigecycline in the CSF of patients was minimal and was far below the typical MIC of tigecycline [11]. Therefore, tigecycline has no effect on CNS MDR/XDR infection. Owing of the unavailability of polymyxin 5 years ago in Mainland China, the treatment of meningitis caused by *Acinetobacter baumannii* with tigecycline in cases 1 and 2 was futile. Their parents brought polymyxin E that was obtained from abroad, and they were subsequently successfully treated. In the past 3 years, polymyxin B has been prescribed in China. Our study was unable to analyze the strengths and weaknesses of polymyxin E and B due to the small number of cases.

Local administration of polymyxin is currently reserved as the treatment option for MDR/XDR GNBM or ventriculitis. For treatment of meningitis, adequate systemically and locally antibiotic administration shall be given early during the entire treatment period. Patients with continuous bacterial growth in CSF culture should be treated with intraventricular therapy (IVT). A recent study [5] suggested that IVT antibiotic in post-neurosurgical GNBM treatment may reduce CSF sterilization time. Three children in our study received intravenous infusion of polymyxin B combined with intraventricular injection of polymyxin B through the Ommaya reservoirs. Timely IVT may improve the clinical cure rate for post-neurosurgical meningitis. Adverse neurologic outcomes are associated with delayed sterilization of the CSF.

Adverse drug effects related to IVT antibiotic treatment include seizure, chemical ventriculitis, or hearing loss. A previous study has shown that the incidence of chemical ventriculitis ranged from 13 to 60% and the incidence of treatment-related seizures ranged from 4 to 20%

Table 2 Antimicrobial susceptibilities and treatment

Case	CSF culture	Antibiotic resistance category	Antibiotic sensitivity	MIC	Intravenous		Intraventricular		Days to CSF sterilization
					Antibiotic	Duration (days)	Antibiotic	Durations	
1	*Acinetobacter baumannii*	XDR	Tigecycline	1	Tigecycline	3	No		26
			Polymyxin	16	Cefoperazone sulbactam	62			
					Polymyxin E	45			
2	*Acinetobacter baumannii*	XDR	Tigecycline	1	Tigecycline	3	No		10
			Polymyxin	4	Cefoperazone sulbactam	22			
					Polymyxin E	22			
3	*Acinetobacter baumannii*	XDR	Tigecycline	4	Tigecycline	8	PolymyxinB	21	22
			Polymyxin	4	Cefoperazone sulbactam	21			
					Polymyxin B	33			
4	*Klebsiella pneumoniae*	XDR	Tigecycline	0.5	Tigecycline	12	PolymyxinB	12	Still positive
			Polymyxin	0.125	Cefoperazone sulbactam	18			
					Polymyxin B	16			
5	*Pseudomonas aeruginosa*	XDR	Amikacin	8	Amikacin	7	PolymyxinB	21	21
			Polymyxin	1	Cefoperazone sulbactam	60			
					Polymyxin B	45			

XDR extensively drug-resistant, *MIC* minimum inhibitory concentration, *CSF* cerebrospinal fluid

[12]. Three patients received IVT polymyxin B through the Ommaya reservoirs in our study, and no side effects occurred. These unconsciousness children received brainstem auditory evoked potentials (BAEP) test that revealed hearing impairment.

To assess the safety and therapeutic efficacy of polymyxin, Sahbudak Bal Z's study [13] showed nephrotoxicity occurred in 10.5% of the patients. Nephrotoxicity occurred between the third and seventh day of treatment and 63% of the nephrotoxicity was induced by polymyxin E. The absence of nephrotoxicity in our patients may be related to the fact that our patients were trauma children without underlying disease. The patients must be tracked for side effects throughout the course of polymyxin treatment, not only during the early stages. It has been documented that the nephrotoxicity of polymyxin is dose-dependent [14]. Our five cases did not show signs of oliguria and renal dysfunction throughout the treatment and follow-up-periods.

There were few studies on the neurotoxicity of polymyxin in critical ill children and the incidence of neurotoxicity ranged from 0 to 2.5% [15]. In our study, it is difficult to determine the neurotoxicity of polymyxin because of the variable consciousness of these children after neurosurgery. The sedatives, analgesic drugs and neuromuscular blockers for critically ill patients can mask the neurotoxicity of polymyxin.

Studies have reported that *Pseudomonas aeruginosa* was a predictor of poor prognosis in newborns and children [16]. *Pseudomonas aeruginosa* were negative impacts of drug resistance and an independent risk factor for mortality [17]. One child infected with *Pseudomonas aeruginosa* had received polymyxin B for 45 days in our study, but she had relapsed after 8 months. It was suggested that more active interventions should be considered, such as earlier IVT therapy for *Pseudomonas aeruginosa* meningitis.

Polymyxin is not covered by medical insurance plans in China. Although polymyxin has been shown to increase clinical cure rates and to reduce mortality of children with XDR meningitis, it is still difficult to be prescribed for treating XDR meningitis especially in children's hospitals due to significant financial burdens of the family.

In conclusion, polymyxin is a safe and effective therapy for post-neurosurgical multidrug-resistant bacillary meningitis in children. No serious adverse effects of polymyxin were observed in this study.

Author contributions JY and DML participated in the design, analyzed data and contributed to the writing of the manuscript. LHT, ZPS, YSY interpreted the results and helped to draft and revise the manuscript. QS

and JF participated in the design and interpreted the results and helped to edit the manuscript. All the authors have read and approved the final version. QS is the guarantor.

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Compliance with ethical standards

Ethical approval This study was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine.

Conflict of interest No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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