Original Article

Efficacy and safety of intraventricular polymyxin B plus continuous ventricular drainage for the treatment of intracranial infection caused by drug-resistant *Acinetobacter baumannii*

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Background: The bacterial resistance rate has risen in recent years, and polymyxin B has been used more frequently to treat severe intracranial infection. This study aimed to investigate the clinical efficacy and safety profiles of intraventricular polymyxin B plus continuous ventricular drainage for the treatment of intracranial infection caused by drug-resistant *Acinetobacter baumannii* (DR-AB).

Methods: A retrospective study was performed on 21 patients who had an intracranial infection caused by DR-AB after neurosurgery at our hospital from May 2017 to July 2020. These patients were treated by intraventricular polymyxin B plus continuous ventricular drainage. The clinical features, treatment, cerebrospinal fluid (CSF)-related indicators, outcomes, and prognosis of these patients were analyzed.

Results: The external drainage tubes inserted into the lateral ventricle were kept unobstructed in all 21 patients. These patients received intraventricular polymyxin B 5 mg/day plus intravenous antibiotics. The treatment with intraventricular polymyxin B lasted for 18.19±12.36 days. The time to positive CSF culture was 10.50±10.60 days. The bacterial clearance rate of CSF was 95.2% (20/21). The clinical cure rate was 81.0% (17/21), and the mortality rate was 19.0% (4/21). As for the causes of death, 1 case died from purulent CSF with cerebral abscess, which was considered to be caused by extensive brain parenchymal infection, 2 cases died from spontaneous intraventricular hemorrhage after returning negative for CSF cultures, and 1 case died from secondary massive cerebral infarction after returning negative for CSF cultures. There were no significant changes in the serum creatinine level before and after treatment.

Conclusions: For intracranial infection caused by DR-AB, early intraventricular polymyxin B plus continuous ventricular drainage could effectively clear the drug-resistant bacteria from CSF, thereby improving efficacy and reducing mortality. Renal functions before and after treatment were not changed significantly, proving that this combined treatment was safe and effective.

Keywords: Polymyxin B; continuous ventricular drainage; dug-resistant *Acinetobacter baumannii* (DR-AB); intracranial infection

Submitted May 14, 2021. Accepted for publication Jan 17, 2022.
doi: 10.21037/apm-21-3149
View this article at: https://dx.doi.org/10.21037/apm-21-3149

Introduction

Acinetobacter baumannii is a gram-negative bacillus and is one of the main pathogens causing intracranial infections after neurosurgery. Drug-resistant *Acinetobacter baumannii* (DR-AB) are resistant to most or the vast majority of common antibiotics, and it is increasing year by year. (1,2). Treating intracranial infection caused by *Acinetobacter baumannii* that is susceptible to only a few antibiotics poses a significant challenge, and is associated with increasingly higher mortality. Polymyxin B, a polypeptide antibiotic (3), was used to treat Gram-negative bacilli in the 1950s, and was later replaced by other antibiotics due to nephrotoxicity. Recently, polymyxin B has been used more frequently to cope with a yearly increase in the rate of bacterial resistance to antibiotics. It has been shown that only a tiny amount of intravenous polymyxin B can enter the cerebrospinal fluid (CSF) and exert an anti-infective effect (4,5). Therefore, intraventricular and/or intrathecal administration may be more effective pathways to treat DR-AB-induced intracranial infection. Different from previous studies, this article only explores the efficacy and safety of intraventricular application of polymyxin B combined with continuous ventricular drainage technology in patients with DR-AB intracranial infection through retrospective analysis, and a detailed analysis of the cause of death for the future Provide basis for clinical work. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3149/rc).

Methods

General data

A total of 21 patients with intracranial infection caused by DR-AB who received treatment at the Aviation General Hospital from May 2017 to July 2020 were recruited. The protocol was approved by the Medical Science Research Ethics Committee of the Aviation General Hospital (No. 2021-KY-01-10). The present study was retrospective and clinical data were collected from patients without interference of the treatment. Therefore, no physiological risks were brought to the patients. The data were collected and treated anonymously. After full discussion by the ethics committee, the patients were exempted from signing informed consent after weighing the risk-benefit ratio, and their confidentiality was protected. The present study followed the principles of the Declaration of Helsinki (as revised in 2013).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) aged above 18 years old; (II) CSF cultures indicated DR-AB (6); (III) conforming to the diagnostic criteria for intracranial infection developed by the Chinese Neurosurgical Society of the Chinese Medical Association (7).

The exclusion criteria were as follows: (I) suspected of DR-AB colonization or contamination; (II) history of intracranial infection before craniotomy; (III) previous treatment with polymyxin B due to intracranial infection or infection of other sites within 3 months; (IV) pregnancy or combined with malignancies outside the central nervous system.

Treatment

The treatment scheme was formulated individually after admission depending on whether the patients had the lumbar cistern drainage tube, ventriculoperitoneal shunt, or external drainage tube inserted into the lateral ventricle. CSF samples were collected for bacterial cultures. Intraventricular polymyxin B 5 mg/day was administered immediately after the presence of DR-AB was indicated by the antimicrobial susceptibility test. (Because the lateral ventricle drainage technique was adopted for cerebrospinal fluid drainage in the cases of this study, polymyxin B was administered intracerebroventricularly).

The types and administration pathways of systemic antibiotics were as follows (depending on the results of the antimicrobial susceptibility test): polymyxin B 50 mg, IV drip, bid; tigecycline (ZeTan, Jiangsu Haosen Pharmaceutical Co, Jiangsu, China) 50 mg, IV drip, bid, after an initial dose of 100 mg; cefoperazone sodium and sulbactam sodium (Xianshu, Suzhou Dongrui Pharmaceutical Co., Ltd, Suzhou, China) 3 g, IV drip, tid; piperacillin sodium and tazobactam sodium (North China pharmaceutical Group Corporation, Shijiazhuang, China) 2 g, IV drip, bid; amikacin (Dali Pharmaceutical Co., Ltd, Dali, China) 0.6 g, IV drip, bid; gentamicin (Shandong Xinhua Pharmaceutical Company Limited, Shandong, China) 80 mg, tid; etimicin sulfate (Xineng, Wuxi Jimin Shanhe Pharmaceutical Co., Ltd, Wuxi, China) 150 mg, bid.

Determination of CSF-related indicators

CSF analysis was conducted using the Hitachi LABOSPECT 008 AS Automatic Analyzer, and glucose, proteins, and chlorine were analyzed. The routine CSF

parameters were analyzed manually since the instruments tended to overestimate the parameters. The BIOMERIEUX Vitek 2 Compact Bacteriological Analyzer was used for bacterial strain identification and the antimicrobial susceptibility test. The results of the antimicrobial susceptibility test were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) antimicrobial susceptibility testing standards M100-S25 [2019]. The susceptibility to polymyxin B was evaluated based on the Food and Drug Administration (FDA) standards.

Data collection

Data were collected retrospectively, including age, gender, underlying diseases, principal diagnosis, name and time of craniocerebral operations before infection, type of systemic antibiotics, bacterial clearance of CSF, and clinical outcomes. Other laboratory test data collected before and after the treatment with polymyxin B included clinical manifestations, white blood cell count, red blood cell count, glucose, chlorine, protein, and liver and kidney function indicators.

Efficacy evaluation

Efficacy was divided into etiological and clinical efficacy. Etiological efficacy was considered if a patient was negative for CSF cultures 3 times consecutively after the treatment. Clinical efficacy was considered if a patient satisfied the following criteria: (I) normal body temperature for at least 3 consecutive days; (II) improvement or disappearance of the initial symptoms (meningeal irritation sign, consciousness); (III) CSF glucose above 2.2 mmol/L 3 times consecutively, with the ratio of white blood cells to red blood cells <1:500. Either was considered as clinical cure.

Safety analysis

Adverse events (AEs) related to medication were closely observed, including anemia, leukopenia, thrombocytopenia, hepatic and renal toxicity, diarrhea, and convulsion. The incidence of AEs was calculated.

Statistical analysis

Descriptive statistical analyses were performed using SPSS v.23.0 software. Continuous measurements were expressed as mean ± standard deviation and medians [interquartile range (IQR)]. The data before and after treatment were compared using the paired *t*-test or Wilcoxon test. Enumeration data were expressed as IQR. $P<0.05$ indicated a significant difference.

Results

Baseline information of the patients

A total of 21 patients were recruited, including 15 males and 6 females, with an average age of 46.33±16.96 years old. All the included patients were referred to our hospital after being diagnosed with intracranial infection at other hospitals. They all had a history of neurosurgery before the infection. The primary diseases and the surgical procedures of these patients are listed in *Table 1*.

Surgical treatment and intracerebroventricular administration

Principles of surgical treatment

The unblocked external drainage tubes inserted into the lateral ventricle upon admission were preserved; the lumbar cistern drainage tubes present upon admission were removed, and external drainage was performed for the lateral ventricle; for those without external drainage tubes inserted into the lateral ventricle upon admission, external drainage was performed for the lateral ventricle; all ventriculoperitoneal shunts upon admission were removed.

Intraventricular administration

The dose of intraventricular polymyxin B was 5 mg/day in all patients. The treatment with intraventricular polymyxin B lasted for 18.19±12.36 days. The time to positive CSF culture was 10.50±10.60 days (*Table 2*).

Results of bacterial testing and systemic medication

The CSF cultures were positive for DR-AB in all patients. There were 6 cases infected with multidrug-resistant *Acinetobacter baumannii* (MDR-AB) and 15 cases with extensively drug-resistant *Acinetobacter baumannii* (XDR-AB). All patients were prescribed systemic antibiotics. The antibiotic schemes varied for different patients, and included tigecycline-cefoperazone sodium and sulbactam sodium (n=8), tigecycline (n=5), tigecycline-etimicin (n=3), tigecycline-amikacin (n=2), polymyxin-cefoperazone sodium and sulbactam sodium (n=1), tigecycline-polymyxin (n=1), tigecycline-piperacillin sodium and tazobactam

Table 1 General information of the enrolled patients

Patients	Outcome
Total	21
Average age (mean ± SD) (years)	46.33±16.96
Gender, n (%)	
Male	15 (71.4)
Female	6 (28.6)
Primary diagnosis, n (%)	
Cerebral hemorrhage	7 (33.3)
Traumatic brain injury	6 (28.6)
Subarachnoid hemorrhage	4 (19.0)
Brain tumor	3 (14.3)
Lupus encephalitis	1 (4.8)
Operation history before infection, n (%)	21 (100.0)
Surgical procedures before infection, n (%)	
LD	16 (76.2)
EVD	13 (61.9)
≥2 times LD, n (%)	6 (28.6)
≥2 times EVD, n (%)	5 (23.8)
Craniotomy, n (%)	14 (66.7)
Evacuation of intracranial hematoma, n (%)	5 (23.8)
Decompressive craniectomy, n (%)	7 (33.3)
VPS, n (%)	1 (4.8)
Intracranial space occupying resection, n (%)	3 (14.3)
Ventriculoscopic surgery, n (%)	1 (4.8)
Interventional surgery for aneurysm, n (%)	3 (14.3)
Aneurysm clipping surgery, n (%)	1 (4.8)

LD, lumbar-cistern drainage; EVD, external ventricular drainage; VPS, ventriculoperitoneal shunt.

sodium (n=1), tigecycline-gentamicin (n=1), and amikacin (n=1). The average duration of systemic antibiotic use was 42.0±27.4 days.

Clinical symptoms before and after treatment and CSF test data

Clinical symptoms before and after treatment and CSF test data are shown in *Table 3*.

Treatment results and complications

The bacterial clearance rate of CSF was 95.2% (20/21) in the 21 patients. The clinical cure rate was 81.0% (17/21), and the mortality rate was 19.0% (4/21). The causes of death were as follows: 2 cases had spontaneous intraventricular hemorrhage after returning negative for CSF cultures, and the disease deteriorated. Both died after they gave up treatment and returned home. One case already had purulent CSF with multiple brain abscesses upon admission. This case was suspected to have extensive brain parenchymal infection. Although the CSF cultures returned as negative after using intraventricular polymyxin B, the fluid drained from the abscess cavity was repeatedly positive. This patient gave up treatment and died after returning home. One case had secondary massive cerebral infarction after the CSF culture returned as negative. This patient gave up treatment and died after returning home. The patients who were cured were followed up for 4 months to 3 years. None of the patients relapsed (*Table 4*).

Safety evaluation

Before and after the treatment with intraventricular

Table 2 Surgical treatment of intracranial infection and intraventricular/intrathecal administration

Surgical treatment and intraventricular/intrathecal administration	Outcome
EVD, n (%)	18 (85.7)
Reserve original EVD, n (%)	7 (33.3)
Remove LD, n (%)	1 (4.8)
Remove VPS, n (%)	1 (4.8)
Polymyxin B-intraventricular administration, n (%)	21 (100.0)
Dosage for polymyxin B, 5 mg/day, n (%)	21 (100.0)
Course of treatment for polymyxin B intraventricular administration, (mean ± SD) (days)	18.19±12.36

EVD, external ventricular drainage; LD, lumbar-cistern drainage; VPS, ventriculoperitoneal shunt.

Table 3 Clinical symptoms and laboratory data of the 21 patients

Clinical symptoms (laboratory data)	Before intraventricular administration	After intraventricular administration	P
T >38 ℃, n (%)	19 (90.5)	2 (9.5)	0
Neck stiffness, n (%)	16 (76.2)	7 (33.3)	0.005
GCS, n (%)			
≥12	1 (4.8)	4 (19.0)	
8–12	1 (4.8)	8 (38.1)	
≤8	19 (90.5)	9 (42.9)	0.004
Creatinine, μmol/L	42.41±16.85	43.33±13.65	0.434
CSF			
Leukocyte, median (interquartile range), $\times10^{-6}$/L	1,620.0 (264.0–11,700.0)	10 (0.5–105.0)	0
Glucose, median (interquartile range), mmol/L	0.77 (0.26–2.07)	3.44 (2.93–3.87)	0
Chloride, mean ± SD, mmol/L	115.62±8.53	118.11±7.08	0.263
Protein, mean ± SD, g/L	2.63±1.49	0.93±0.55	0

GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid.

Table 4 Outcome of the 21 patients

Outcome	Data
Clinical cure rate, n (%)	17 (81.0)
Pathogen clearance rate, n (%)	20 (95.2)
CSF bacteria negative time, mean ± SD (days)	10.50±10.60
Death, n (%)	4 (19.0)
Cerebral hemorrhage	2 (9.5)
Brain parenchymal infection	1 (4.8)
Large cerebral infarction	1 (4.8)

CSF, cerebrospinal fluid.

polymyxin B, the serum creatinine levels were 42.41±16.85 and 43.33±13.65 μmol/L, respectively, indicating no significant difference (P=0.434). No kidney function impairment was observed.

Discussion

Intracranial infection is a common and severe complication after neurosurgery (8,9), which may lead to prolonged hospital stay, increased medical costs, or even death. The incidence of intracranial infection varies between 0.72% and 8% (10). Intracranial infection most often occurs after craniocerebral operations. External ventricular drainage and lumbar cistern drainage after surgeries for intracranial tumors, severe craniocerebral injury, cerebroventricular hemorrhage, subarachnoid hemorrhage, and hydrocephalus may lead to the damage of the blood-brain barrier and the decline of immune system function in critically ill patients, which are the leading causes of intracranial infection (11). All patients included in the present study had a history of neurosurgery, typically lumbar cistern drainage, external ventricular drainage, and craniotomy. The main pathogens of intracranial infection were identified as Gram-positive cocci and Gram-negative bacilli. The AB-induced infection rate after neurosurgery is as high as 15–21.74% (2). The incidence of intracranial infection and the prevalence of drug-resistant bacteria continue to rise, which poses a challenge to clinical treatment.

Common medications against Ab-induced infections include sulbactam, cephalosporin, carbapenems, β-lactams, aminoglycosides, fluoroquinolones, tetracyclines, and polymyxin. However, only a limited number of antibiotics are potent against DR-AB. Upon admission, the antimicrobial resistance rates for carbapenems, cephalosporins, and aminoglycosides reached up to 95.2%, 100%, and 90.5% among our patients, respectively, which might be related to the prior use of large-dose high-grade antibiotics at other hospitals. DR-AB strains are known for their extremely high drug resistance, which is related to treatment difficulty and poor prognosis. It is urgent to look

for antibiotics that are unlikely to cause drug resistance.

Polymyxin B is a rapid-acting bactericidal agent, which exhibits good activity against the vast majority of Gram-negative bacteria (12). It was once replaced by safer antibiotics due to its narrow antibacterial spectrum and significant nephrotoxicity. In recent years, infections caused by multidrug-resistant Gram-negative bacteria have become widespread worldwide, which has necessitated the reemergence of polymyxin B (13). It has been shown that polymyxin B is effective against various severe nosocomial infections caused by Ab, including bacteremia, urinary tract infection, and pulmonary infections (14). However, polymyxin B can hardly penetrate the blood-brain barrier to reach an effective inhibitory concentration in CSF due to its high molecular weight. Few reports have been published at home and abroad regarding the use of polymyxin B in intracranial infection.

According to the Chinese Expert Consensus on the Diagnosis and Treatment of Infection in Neurosurgical Critically Ill Patients [2017] developed by the Chinese Neurosurgical Society of the Chinese Medical Association and the Chinese Collaboration Group for Infection Diagnosis and Treatment in Neurosurgical Critically Ill Patients in 2017 (7), intraventricular/intrathecal administration is effective for treating intracranial infection, especially when patients are unresponsive to systemic intravenous antibiotics. The above administration pathway bypasses the blood-brain barrier and directly delivers the antibiotics to the sites of infection. Therefore, the drugs can work more directly and effectively while preventing the toxic reactions associated with systemic antibiotic use (15). Given the facts above, intraventricular/intrathecal polymyxin B may be a good alternative for the treatment of DR-AB-induced intracranial infection. It has been reported that the use of polymyxin B alone may be related to poor outcomes (16). In contrast, the combined use of other antibiotics can significantly enhance the effectiveness and reduce mortality (17). At present, there has been no uniform standard for the treatment cycle in patients with severe intracranial infection. The treatment may last for as long as 4–8 weeks. We recruited a total of 21 patients with DR-AB-induced intracranial infection after neurosurgeries, all of which received intraventricular polymyxin B for 18.19±12.36 days and combined intravenous administration of several sensitive antibiotics for 51.14±29.68 days. The bacterial clearance rate of CSF reached up to 95.2% (20/21), and the clinical cure rate was 81.0% (17/21). The results showed that intraventricular polymyxin B could effectively eliminate DR-AB from CSF, working synergistically with intravenous antibiotics.

According to a recent report, the mortality of DR-AB-induced intracranial infection was markedly high, reaching up to 40.3%(18). In our study, the overall mortality was 19.0% (4/21). The mortality directly caused by the infection was 1/21 (4.8%). Both were lower than the levels reported in the literature. This might be due to the early use of intraventricular polymyxin B after the discovery of DR-AB. Wang *et al.* also reported that early, effective intraventricular drug administration could improve the cure rate of intracranial infections after neurosurgeries (19).

However, polymyxin B has considerable nephrotoxicity, neurotoxicity, and neuromuscular blocking effects. One recent study demonstrated that the incidence and severity of nephrotoxicity associated with polymyxin B were actually low (20). Besides, these side effects were reversible after discontinuation (21). During treatment, these AEs did not affect any of our patients. The serum creatinine levels before and after treatment were 42.41±16.85 and 43.33± 13.65 μmol/L, respectively, without a significant difference ($P>0.05$). Thus, the treatment scheme had a favorable safety profile for DR-AB-induced intracranial infection.

In addition to intracerebroventricular administration, the necessary surgical methods are particularly important in the treatment of intracranial infections. For example, early removal of infection-related artificial materials (7,22) and continuous cerebrospinal fluid drainage (23). Ventricular drainage and lumbar cistern drainage are currently commonly used methods of cerebrospinal fluid drainage. Some scholars believe that lumbar cistern drainage can better reduce the recurrence of intracranial infections. The lumbar cistern drainage tubes are generally narrow. The DR-AB-infected CSF is turbid, contains floccules, and may even become purulent, blocking the drainage tube and increasing the risk of infection. The previous research of our research team showed that the extraventricular drainage tube may be more suitable for drainage of purulent cerebrospinal fluid due to its thicker tubing (24). Among the 21 patients in the present study, 1 patient had a lumber cistern drainage tube and 1 patient had a ventriculoperitoneal shunt upon admission. Both were removed after admission. Another 7 patients did not have their external ventricular drainage tubes removed upon admission since the tubes were maintained unblocked and were later used to drain inflammatory CSF and to administer the drugs intraventricularly. These drainage tubes were removed after the infection was controlled

properly. Overall, continuous, unblocked CSF drainage can effectively remove the bacteria-infected CSF outside the body. The drainage tubes should not be replaced or removed prematurely or frequently to avoid secondary injury to brain tissues and the central nervous system, thereby reducing intracranial hemorrhage.

Conclusions

For DR-AB-induced intracranial infection, early treatment with intraventricular polymyxin B plus continuous external ventricular drainage could effectively clear DR-AB from CSF, thereby improving efficacy and reducing mortality. There were no significant changes in renal function before and after treatment, indicating a favorable safety profile of this treatment scheme. However, these findings need to be further corroborated in large-scale studies in the future.

Our study also had the following limitations: we did not comprehensively analyze the antibacterial activity of polymyxin B, drug concentration in CSF, or optimal drug dose for DR-AB-induced intracranial infection.

Acknowledgments

Funding: We acknowledge the support received from Scientific Research Project of Aviation General Hospital of Beijing (YJ202021).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3149/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3149/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3149/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study followed the principles of the Declaration of Helsinki (as revised in 2013). This study has been approved by the Medical Science Research Ethics Committee of Aviation General Hospital (No. 2021-KY-01-10). The patients were exempted from signing informed consent.

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(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Chen L, Li X, Li D, Dong X, Chen H. Efficacy and safety of intraventricular polymyxin B plus continuous ventricular drainage for the treatment of intracranial infection caused by drug-resistant *Acinetobacter baumannii*. Ann Palliat Med 2022;11(2):490-497. doi: 10.21037/apm-21-3149

