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Case Report

Successful intraventricular colistin treatment in resistant *Klebsiella pneumoniae* meningitis

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Abstract

Meningitis due to resistant microorganisms after neurosurgical intervention progresses with significant morbidity and mortality. Treatment is difficult as the antibiotics available for this purpose as well as their transition to the cerebrospinal fluid are limited. Due to the inability of the intravenously administered colistin to cross the blood–brain barrier sufficiently, intraventricular colistin application is recommended in the treatment of meningitis. Herein we report successful treatment with intraventricular colistin of an infant with ventriculoperitoneal shunt-related meningitis due to extended spectrum β-lactamase-producing *Klebsiella pneumoniae.* The infant lacked clinical response despite effective intravenous antibiotic therapy. Intrathecal/intraventricular colistin can be an effective alternative in the treatment of resistant Gram-negative bacilli meningitis.

Key words: *Klebsiella*; meningitis; antimicrobial resistance; intraventricular colistin.

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Introduction

Post-neurosurgical meningitis and ventriculitis are the most important complications of surgical procedures [1,2] The need for long-term hospitalization, high treatment costs, higher risk of encountering resistant microorganisms, and the limited number of antibiotics that can be used in treatment due to the blood–brain barrier are important aspects to be considered [1]. The increasing number of resistant microorganisms restricts treatment options. Colistin seems to be an effective treatment option, especially in Gram-negative bacterial infections with multiple drug resistance. The inability of the intravenously administered colistin to cross the blood–brain barrier sufficiently suggests intraventricular colistin application in the treatment of meningitis [3].

Although intraventricular antibiotic use has long been described in the literature, there is insufficient evidence for routine applications. It presents the advantages of acting without having to cross the blood–brain barrier, causing no systemic side effects, and reaching high concentrations in the cerebrospinal fluid (CSF). However, not enough information exists about the dose and risk of secondary infection [2]. The absence of a randomized controlled study on the efficacy and safety of intraventricular colistin use in pediatric patients prevents its routine use. This report presents a successful clinical response of intraventricular colistin therapy application to treatment of postsurgical meningitis that lacked clinical response despite effective intravenous antibiotic therapy.

Case report

An 11-month-old girl was brought to our clinic with persistent fever for about six days. There were no other complaints. Physical examination showed that she was conscious but restless, had weak head control, could not sit without support, and presented extensive hypotonicity in the bilateral lower extremity. There was no pathology except neuromotor developmental retardation. Her body temperature, heart rate, respiratory rate, and arterial blood pressure were 39.5 °C, 177/min, 32/min, and 80/50 mm Hg, respectively. The patient had undergone a ventriculoperitoneal (VP) shunt operation about two weeks ago with diagnosis of congenital hydrocephalus and meningomyelocele. Laboratory findings revealed a leukocyte count of 13,900/mm^3 (65% neutrophils and 35% lymphocytes), C-reactive protein of 20.1 mg/dL, and an erythrocyte sedimentation rate of 91 mm/hour. Kidney and liver

function tests were normal, and urinalysis revealed no pathology. CSF was taken from the VP shunt pump. The color of the CSF was clear, and protein, glucose, and simultaneous blood sugar levels were 71.8 mg/dL, 37 mg/dL, and 84 mg/dL, respectively. Microscopic examination of the CSF detected 20 leukocytes/mm^3. Intravenous cefotaxime (300 mg/kg/day) treatment was started. On the third day of hospitalization, vancomycin was added to the treatment after her fever did not regress. However, an angioedema developed after the use of vancomycin, and thus, it was stopped and linezolid was started. The CSF culture grew extended spectrum β-lactamase-producing carbapenem-resistant *Klebsiella pneumoniae*. The mean inhibitory concentration values for meropenem, cefepime, ciprofloxacin, colistin, amikacin, and tigecycline were > 16, > 32, > 4, ≤ 0.5, ≤ 2, and 2 μg/mL, respectively. Cefotaxime and linezolid therapy were discontinued, and meropenem and colistin were started. Upon continued growth of *K. pneumoniae* in the control CSF culture taken on the 5th day of this treatment, the VP shunt was removed and external ventricular drainage was inserted. The fever continued on the 10th day of the meropenem and colistin treatment, namely 5 days after the VP shunt was removed. Given the lack of response to the intravenous antibiotic therapy and the continued growth of *K. pneumoniae* in the CSF cultures taken four times at intervals, intraventricular colistin treatment was started. Colistin (5 mg) was administered once daily via the external ventricular drainage, and CSF equal to the amount of colistin administered was removed to prevent intracranial pressure increase. After the colistin application, 1.5 mL of saline was flushed through the catheter to remove any remnants of the drug. The catheter was then clamped for 1 hour. The fever disappeared at the 24th hour of intraventricular therapy. On the 7th day of intraventricular therapy, the CSF proteins regressed from 270 to 120 mg/dL. No bacterial growth was observed in the CSF culture taken on the third day of intraventricular treatment. The treatments with meropenem/colistin and intraventricular colistin were completed over 27 and 14 days, respectively. Patient follow-up protocol are presented in Table 1. While the clinical condition of the patient improved rapidly, no side effects like seizures or chemical ventriculitis were noted during intraventricular colistin application. A radiological examination was done at the end of the treatment before a new VP shunt insertion procedure. Bilateral lateral ventricles and third ventricle dilatation consistent with hydrocephalus and the brain parenchyma atrophy secondary to hydrocephalus were detected on computed tomography examination.

Discussion

Although VP shunt replacement forms the basis of hydrocephalus treatment, every surgical intervention presents a risk of infection. A study of 7071 patients reported an infection frequency of 11.7% per patient and 7.2% per intervention in a 2-year follow-up after VP shunt insertion. Young age, female gender, presence of shunt secondary to intraventricular hemorrhage, chronic respiratory problem, and multiple revision surgeries were evaluated as risk factors for the development of infection [4].

Table 1. Timeline of patient follow-up protocol.

	Day 0	Day 3	Day 4	Day 9	Day 14	Day 16	Day 21	Day 27	Day 31	Day 32
Presence of fever	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
CSF analysis	Protein: 71.8 mg/dL Glucose: 37 mg/dL 20 WBC/mm^3	Protein: 87 mg/dL Glucose: 20 mg/dL 10 WBC/mm^3		Protein: 58 mg/dL Glucose: 20 mg/dL 0 WBC/mm^3	Protein: 270 mg/dL Glucose: 19 mg/dL 0 WBC/mm^3		Protein: 126 mg/dL Glucose: 17 mg/dL 0 WBC/mm^3		Protein: 61 mg/dL Glucose: 22 mg/dL 0 WBC/mm^3	
Medical therapy and interventions	Start Cefotaxime	Start Vancomycin (angioedema developed and discontinued) Start linezolid	Stop Cefotaxime and linezolid Start meropenem and colistin	VP shunt was removed and external ventricular drainage was inserted	Start Intrathecal colistin			Stop Intrathecal colistin	Stop Meropenem	New VP shunt insert

CSF: cerebrospinal fluid; VP: ventriculoperitoneal shunt; WBC: white blood cell.

Central nervous system (CNS) infections due to multi-drug resistant microorganisms are being increasingly reported [5,6]. The mortality rate in these CNS infections is high [6-8]. Colistin treatment can be successful in carbapenem-resistant Gram-negative infections. However, a risk of nephrotoxicity remains even when intravenous colistin treatment is administered in appropriate doses. In addition, low blood brain barrier penetration leads to low dose drug concentration in the infection area and a decrease in treatment success [5,9]. Markantonis *et al*. showed that only 5% of the intravenously applied colistin passes to the CNS [3]. Additionally, after intravenous colistin treatment, the colistin concentration measured in CSF was below 5 mcg/mL, while the CSF concentration after intraventricular or intrathecally applied colistin exceeded 5 mcg/mL [10]. The limited transition of intravenously administered colistin therapy to CSF is considered as one of the important causes of treatment failure. Therefore, treatment of intrathecal/intraventricular colistin is seen as an alternative therapy in Gram-negative CNS infections with multiple drug resistance [5,9]. No randomized controlled trials including a large pediatric-age patient group have been conducted. The available data are mostly sourced from adult studies involving a small number of cases.

The 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis recommends intraventricular antibiotherapy in cases that are not responsive to systemic antibiotic therapy. It is recommended that the drug dose be adjusted according to the ventricular volume, volume of CSF discharged from the ventricle daily, and the microorganism's mean inhibitory concentration values for antibiotics. In adults, treatment with intraventricular colistin (as 10 mg of colistin methanesulfonate) is recommended. As the ventricular volume in a child is lower, 60% of the adult dose is suggested for a child [11]. In order to prevent intracranial pressure increase, it is recommended that CSF is removed to the same extent as the amount of drug administered, and that a saline flush is performed after the drug is given to prevent any remnants of the latter in the catheter [12].

In a study evaluating 33 adult patients diagnosed with carbapenem-resistant *Acinetobacter baumannii* postoperative meningitis, 17 cases were given intrathecal/intraventricular colistin in addition to intravenous colistin, while the remaining 16 were administered only intravenous colistin. The cost of treatment, length of stay in the hospital/intensive care unit, and duration of ventilator treatment were significantly lower in the in the group receiving intrathecal/intraventricular colistin. Mortality rates were also lower but there was no significant difference. Despite the development of chemical meningitis in three of the patients, spontaneous improvement was observed in their two-week follow-ups [1].

A meta-analysis on the treatment of post-neurosurgical *A. baumannii* infections showed that mortality was 84% lower in the group receiving intravenous and intrathecal therapy compared to that receiving only intravenous therapy [12]. However, a systematic review in 2014 found that not enough data existed to routinely recommend a combination of systemic and intrathecal antibiotics in pediatric VP shunt infection cases [13].

Khan *et al.* studied 21 cases diagnosed with post-operative meningitis/ventriculitis, who were given intraventricular amikacin, polymyxin B, or colistin treatment according to the antibiotic susceptibility of the active microorganism. Successful results were obtained in 95% of the cases. Sterilization in CSF was achieved between 2 and 16 days, and no side effects related to the intrathecal/intraventricular therapy were observed [2].

Although *K. pneumoniae* detected in our case was sensitive to colistin therapy and the VP shunt was removed, the patient did not respond to intravenous meropenem and colistin treatment. Positive clinical response in a short time with intraventricular therapy supports the idea that intrathecal/intraventricular colistin may be applied in meningitis cases unresponsive to intravenous therapy. Extensive studies are needed to ascertain routine use in the pediatric patient group.

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