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Case Report

Intraventricular Antimicrobial Therapy for Intractable Ventriculitis: Two Case Reports

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

It is challenging to treat ventriculitis with parenteral treatment alone in some cases because of the difficulty involved in maintaining an appropriate level of antibiotics in cerebrospinal fluid (CSF). We report two cases of ventriculitis who did not respond to intravenous (IV) antibiotics but were successfully treated with intraventricular antibiotics using IV agents. The first case was a four-month-old male patient with X-linked hydrocephalus. He showed ventriculitis due to *Klebsiella pneumoniae* not producing extended-spectrum β-lactamase and susceptible to third-generation cephalosporins and gentamicin, following ventriculoperitoneal (VP) shunt. His condition did not improve during the 47 days of treatment with IV cefotaxime and meropenem. We achieved improvement in clinical presentation and CSF profile after three times of intraventricular gentamicin injection. The patient was discharged from the hospital with antiepileptic drugs. The second case was a six-month-old female patient with a history of neonatal meningitis complicated with hydrocephalus at one month of age, VP shunt at two months of age, followed by a methicillin-resistant coagulase-negative staphylococci (CoNS) shunt infection with ventriculitis after the shunt operation. CoNS ventriculitis recurred four weeks later. We failed to treat intractable methicillin-resistant CoNS ventriculitis with IV vancomycin for ten days, and thus intraventricular antimicrobial treatment was considered. Five times of intraventricular vancomycin administration led to improvement in clinical parameters. There were only neurological sequelae of delayed language development but no other major complications. Patients in these two cases responded well to intraventricular antibiotics, with negative CSF culture results, and were successfully treated for ventriculitis without serious complications.

Keywords: Injections, intraventricular; Cerebral ventriculitis; Central nervous system infections

INTRODUCTION

Ventriculitis is the inflammation of the ventricular fluid and the ependymal lining of the ventricles. There is no standardized definition for ventriculitis. It is usually secondary to infections such as meningitis, abscess, trauma-related infections, or healthcare-associated infections.[1,2] Cerebrospinal fluid (CSF) studies including culture and neuroimaging should be performed.[1-3] Systemic antimicrobials based on the CSF culture results are the treatment for ventriculitis.[1] However, the blood-brain barrier (BBB) and blood-CSF barrier

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function as lipid layers in the CSF compartment, which may be a challenge in achieving therapeutic antimicrobial concentrations in the central nervous system (CNS) via intravenous (IV) treatment alone.[1,4,5] Intraventricular antibiotic treatment enables to obtain the CSF concentration to the desired levels with a low potential for systemic toxicity.[1,5-7] It allows direct access to the extracellular central nervous compartments by bypassing anatomical barriers, and high CSF drug levels can be attained with relatively small doses.[1,5,8] It is indicated for patients with ventriculitis or meningitis as an adjunctive therapy refractory to IV antibiotics and have limited antimicrobial treatment options due to poor CSF penetration.[1,4,5,9] Here, we report the successful treatment of intractable *Klebsiella pneumoniae* and coagulase-negative staphylococci (CoNS) ventriculitis using intraventricular and IV antibiotics.

CASE

1. Case 1

A Korean four-month-old male patient with X-linked hydrocephalus was admitted to the emergency room with complaints of fever and abdominal distension. This patient had been diagnosed with congenital hydrocephalus. Magnetic resonance imaging (MRI) of the brain showed aqueductal stenosis and suspicious cortical dysplasia involving the parieto-occipital cortex. He underwent endoscopic third ventriculotomy five days after birth and ventriculoperitoneal (VP) shunt operation at two months of age. In the emergency room, he presented with bulging anterior fontanelle over the subcutaneous shunt tubing area on physical examination. He revealed hypotonia, adducted thumbs, and rigid distal interphalangeal joint of the index fingers. His laboratory tests showed markedly elevated erythrocyte sedimentation rate and C-reactive protein levels of 54 mm/hr (normal, 0–20 mm/hr) and 28.44 mg/dL (normal, 0–0.5 mg/dL), respectively. The CSF analysis demonstrated an elevated white blood cell (WBC) count and protein level, and low glucose level suggesting possible bacterial infection (WBC 2,200 /μL, protein level of 140.5 mg/dL with turbid color, glucose less than 2 mg/dL (CSF/serum glucose ratio: <0.02)). Initial brain computed tomography (CT) showed features of ventriculitis due to increased hydrocephalus of the lateral ventricle and debris of the occipital horns (**Fig. 1A**). Abdominal CT showed findings of small bowel mechanical obstruction.

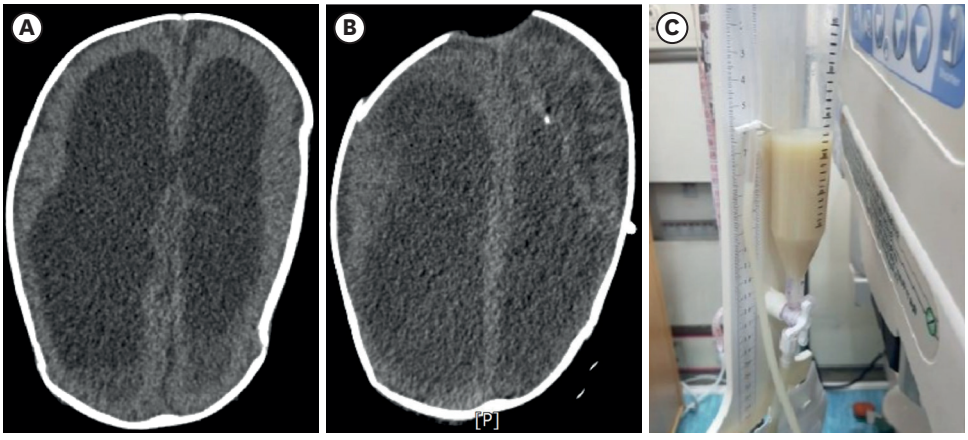

Fig. 1. Findings of case 1 patient. (A) Brain CT (HD 5) shows debris in the occipital horns, increased hydrocephalus, and ventriculitis. (B) Brain CT (HD 45) shows multiple septations formed inside the ventricles, both EVDs functioning well without midline shift. (C) The color of the cerebrospinal fluid from the EVD; flow chamber became turbid as the patient developed fever (HD 45).
Abbreviations: CT, computed tomography; HD, hospital day; EVD, external ventricular drain.

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Suspecting VP shunt infection and peritonitis, treatment with IV meropenem (40 mg/kg/dose every 8 hours; infused over 3 hours) was initiated in addition to an emergent shunt removal operation. *K. pneumoniae* not producing extended-spectrum β-lactamase and susceptible to third-generation cephalosporins and gentamicin was isolated from the initial CSF and VP shunt tip culture during the operation. Therefore, IV meropenem was changed to cefotaxime (50 mg/kg/dose every 6 hours). Serial CSF analysis was performed using an external ventricular drain (EVD) catheter with WBC counts of CSF continuously higher than 2,000 /μL, glucose levels of CSF remaining below 10 mg/dL. *K. pneumoniae* was consistently isolated from the CSF culture until the 17th day of the appropriate IV antibiotic maintenance.

The patient presented with a sudden onset of fever (38.3°C), seizures, and altered mental status on hospital day 45. Brain CT imaging showed multiple septations inside the ventricles (**Fig. 1B**), implying aggravation of ventriculitis and turbidity of the CSF drainage (**Fig. 1C**). He underwent an endoscopic ventricular irrigation operation, and the entire ventricle was filled with pus. Maintenance therapy with IV cefotaxime and meropenem for 47 days did not improve the patient's condition. Although his clinical symptoms and the CSF profile aggravated, the pus culture and subsequent CSF culture results were continuously confirmed to be negative. Intraventricular gentamicin was administered based on in vitro susceptibility to target *K. pneumoniae* because using systemic antibiotics alone responded poorly. A dosage of 2 mg/day of intraventricular gentamicin was administered aseptically in both ventricles on hospital days 48, 50, and 53. We drained a volume of 3 mL of CSF through the EVD catheters before the administration. A dosage of 1 mg of gentamicin and 3 mL of normal saline were aseptically mixed, and this mixed solution was each injected by a slow push through the right and left EVD catheters. The EVD catheters were clamped about one hour after the injection procedure. Intraventricular antibiotic administration was discontinued without further treatment due to a change in his vital signs due to central line infection. We kept maintaining negative CSF culture results and achieved improvement in clinical presentation. The EVD catheters were turbid but became clear, functioning well without additional squeezing or irrigation techniques after hospital days 52–53. Intermittent seizures improved after hospital day 62. After the third intraventricular injection on hospital day 53, we changed IV antibiotics to meropenem (40 mg/kg/dose every 8 hours; infused over 3 hours), maintaining it for about five weeks until the final CSF study. The CSF profile is described in **Table 1**: the CSF WBC counts decreased to 1 /μL, while the CSF protein level decreased to 80 mg/dL, and the CSF glucose level was in the normal range in the final CSF study performed on hospital day 85. The patient was discharged from the hospital with antiepileptic drugs. The patient attended the scheduled outpatient follow-up visits for only four months after treatment. His general condition was relatively good at the last follow-up visit, without any findings suggestive of recurrence of ventriculitis or increased intracranial pressure.

Table 1. The cerebrospinal fluid profile of case 1 during hospitalization (intraventricular gentamicin was injected on HD 48, HD 50, and HD 53)

HD	Right EVD			Left EVD			Lumbar puncture results		
	WBC counts (/μL)	Protein level (mg/dL)	Glucose level (mg/dL)	WBC counts (/μL)	Protein level (mg/dL)	Glucose level (mg/dL)	WBC counts (/μL)	Protein level (mg/dL)	Glucose level (mg/dL)
45	5,600	1,793	17.2	8,400	2,174	11.5			
47	6,400	1,919	41.8	1,650	2,173	8.0			
50	500	396	<2	2,040	922	52.2			
53	24,000	1,239	17.9	60	1,727	32.1			
55	9,600	1,467	2.1	50	1,229	4.6			
56	7,000	1,019	<2	375	Undetectable	Undetectable			
85							1	81	53.4

Abbreviations: HD, hospital day; EVD, external ventricular drain; WBC, white blood cell.

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2. Case 2

An Ethiopian six-month-old female patient was admitted due to fever and vomiting. The patient presented with bulging fontanelle along with diffuse abdominal tenderness. She had a history of neonatal meningitis complicated by hydrocephalus without a culture-proven pathogen at one month of age. She underwent VP shunt operation at two months and was monitored closely during follow-up hospital visits thereafter. A methicillin-resistant *Staphylococcus epidermidis* shunt infection with ventriculitis developed at four months of age treating her with a full 6-week course IV antibiotic therapy. We maintained IV vancomycin for six weeks. Vancomycin dosing was modified according to the therapeutic drug monitoring and the patient's renal function. However, dose adjustment was very challenging due to inconsistency in serum vancomycin trough concentrations. The serum vancomycin trough levels were between 3.5 μg/mL and 12.5 μg/mL in the first eighteen days of antibiotic use: the initial vancomycin dosage of 15 mg/kg/dose every 6 hours, adjusting to 21 mg/kg/dose every 6 hours. Subsequent dose adjustments were made, but the trough levels rose to a potential toxic concentration of 36.9 μg/mL, and the patient presented acute renal failure and a fluctuation in creatinine clearance. The trough levels were maintained between 8.8 μg/mL to 15.3 μg/mL in the next five days but varied between 14.6 μg/mL and 34.7 μg/mL for the next two weeks, accompanying renal failure. The trough levels ranged between 5.1 μg/mL and 6.4 μg/mL in the last week of IV vancomycin use with a final vancomycin dosage of 11.5 mg/kg/dose every 8 hours. The duration of outpatient follow-up visits after treatment discontinuation was one month.

CSF analysis was performed from the shunt reservoir area for suspected ventriculitis relapse. Initial laboratory findings showed elevation of inflammatory markers, and empirical antibiotics including IV vancomycin (15 mg/kg/dose every 6 hours) and IV cefotaxime (150 mg/kg/day every 6 hours) were initiated. Subsequently, *S. epidermidis* resistant to methicillin and susceptible to vancomycin was isolated from the initial CSF culture. Brain MRI and CT showed post-infectious hydrocephalus with no significant change compared to the previous study. The serum vancomycin trough level was 8.5 μg/mL at hospital day 5, and we adjusted the vancomycin dosage to 18 mg/kg/dose every 6 hours. During treatment with IV vancomycin for ten days, hydrocephalus was aggravated, leading to brain stem compression. The patient underwent a shunt catheter removal operation. During the operation, the color of the CSF was found out to be very turbid, and the culture from the distal portion of the removed shunt catheter confirmed the same pathogen.

The serum vancomycin trough concentration measured on the day of operation was 5.0 μg/mL, whereas the CSF vancomycin level during the operation was less than 2.0 μg/mL, which implied poor CNS penetration of vancomycin. Thus, intraventricular vancomycin treatment was considered assuming the failure of conventional IV vancomycin treatment. Intraventricular vancomycin was administered at 10 mg/dose for three days (on the 11th, 12th, and 13th days of hospitalization) through an EVD catheter by a slow push method every 24 hours. We skipped intraventricular vancomycin due to high CSF drug levels on the 14th day of hospitalization. After administration at a 5 mg/dose on the 15th day, the EVD catheter was self-removed accidentally. A new VP shunt was placed on the 18th day of hospitalization, and intraventricular vancomycin was administered at a dose of 5 mg during the operation. We confirmed the result of CSF culture performed on the 11th day just before the intraventricular vancomycin administration sterile. The CSF vancomycin levels were trough levels, measured immediately before the intraventricular injection procedures. Vancomycin trough levels in serum and CSF increased after the treatment (**Fig. 2**). There were no further adjustments in IV vancomycin dosage. IV vancomycin was maintained for a total of four weeks during

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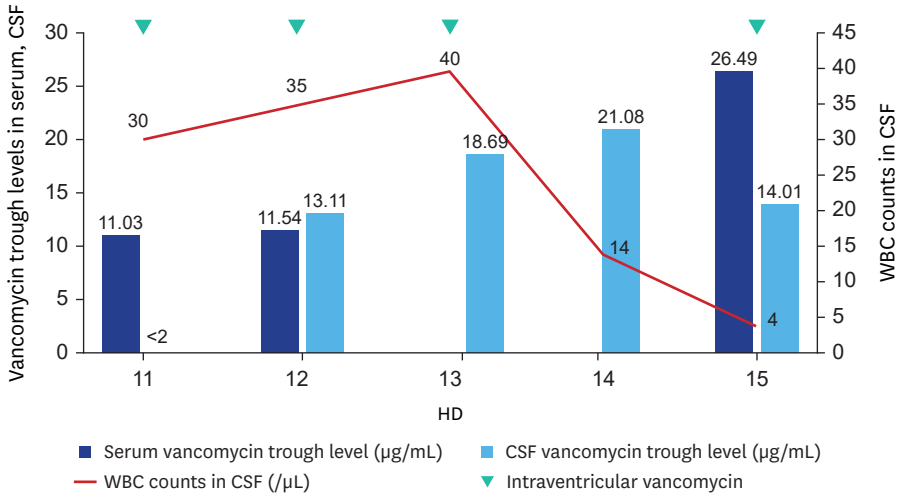

Fig. 2. Vancomycin trough levels in serum and CSF, and WBC counts in CSF of case 2. Vancomycin trough levels in serum and CSF both increased after intraventricular vancomycin administration. A decrease in CSF WBC counts is also notable (yellow arrowheads: intraventricular vancomycin was injected on HD 11, HD 12, HD 13, and HD 15). Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell; HD, hospital day.

hospitalization. There were only neurological sequelae of delayed language development but no other major complications after hospital discharge. There was no recurrence for at least more than four years after the end of treatment.

This study was approved by the Institutional Review Board (IRB) of Korea University (IRB number 2021AS0087).

DISCUSSION

The BBB and the blood-CSF barrier function as lipid layers surrounding the CNS.[4,5] Intraventricular antimicrobial treatment, which bypasses these anatomical barriers, is an effective strategy to treat CNS infections. In our cases, IV antibiotics were inadequate to treat intractable ventriculitis. Intraventricular and parenteral routes of antibiotic administration were effective. Further, as shown in the second case, CSF vancomycin concentrations increased after the injection of intraventricular vancomycin.

The dosage of intraventricular antimicrobial agents was used empirically, and the precise dosage was unavailable. Individual dosage and dosing intervals of the intraventricular drug are based on the CSF drug level, which is 10–20-fold higher than the minimum inhibitory concentration (MIC) of the pathogen, ventricular size, or CSF space, and daily output of the ventricular drain or clearance from CSF.[1,5]

The usual recommended dosages of antibiotics administered by the intraventricular route are as follows: gentamicin 4–8 mg daily in adults and 1–2 mg in children, and vancomycin 5–20 mg daily.[1] Antibiotic dosage in infants should be reduced at least 60% concerning the CSF volume.[1,6] Based on CSF volume or ventricle size, dosage recommendations in adults are as follows: 5 mg vancomycin and 2 mg gentamicin in slit ventricles; 10 mg vancomycin and 3 mg gentamicin in normal-sized ventricles; 15–20 mg vancomycin and 4–5 mg gentamicin in enlarged ventricles.[1] The frequency of administration also matters. The dosing interval

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based on the amount of the CSF output over 24 hours is recommended as follows: once every second day for 50–100 mL; once daily for 100–150 mL; dose escalation for amounts over 150 mL.[1] In one study of 13 neonates, therapeutic CSF drug concentrations were maintained with 5 mg/day vancomycin injected once daily.[10]

We estimated the usual dosage for infants with normal-sized ventricles for approximately 2–10 mg vancomycin and 1–2 mg gentamicin. Concerning that our patients were both infants with enlarged ventricle sizes, we initiated an upper limit dosage. We used 10 mg of intraventricular vancomycin and 2 mg of intraventricular gentamicin. Because daily CSF drainage output over 24 hours of our patients was approximately 100–150 mL, we initiated intraventricular administration once daily. Since vancomycin was capable of therapeutic drug monitoring, we monitored the serum and CSF vancomycin levels.

When the antimicrobial is administered via a ventricular drain during the treatment, the drain should be clamped for 15–60 minutes to achieve equilibrium.[1,11] Also, an aseptic drug delivery technique is critical when this type of invasive therapy is instituted.[11]

The pharmacokinetics, safety, and efficacy of intraventricular antimicrobial treatment have been studied since the introduction of this practice.[6,9,11,12] It is generally known that intraventricular or intrathecal administration of agents such as polymyxin B, colistin, gentamicin, and vancomycin is unrelated to severe or irreversible toxicity.[4-6] Earlier studies suggest that inappropriate dosing may lead to concentration-related toxicity.[4] Reduced consciousness, prolonged headache, seizures, ototoxicity, and CSF eosinophilia were reported after intraventricular antibiotic administration, but none of them were detected in our cases.[12,13] One systematic review reported the safety and effectiveness of using intraventricular aminoglycosides in sensitive gram-negative meningitis, ventriculitis, and CNS device-associated infections.[12]

Several case reports of successful intraventricular antimicrobial treatments of CNS infections have been published in the last decades.[5-7,14-16] The sterilization of CSF and the normalization of CSF parameters were achieved rapidly via the combined use of intraventricular and IV routes when compared with IV route alone.[4,8,15,17,18] A previous multicenter retrospective cohort study suggested that CSF culture sterilization occurred in 88.4% of the 105 patients who were admitted to intensive care units and received intraventricular antibiotic treatment at 11 centers in the United States between 2003 and 2013.[16] There were no relapses in one large study of patients with gram-negative bacillary neurosurgical ventriculitis or meningitis.[17] The combined IV and intraventricular use of vancomycin may improve the CSF levels of vancomycin without side effects at the same dose, and without the need for additional vancomycin.[19]

As far as we know, there are several case reports of intraventricular vancomycin treatment.[9,19] Based on a review of intra-CSF antibiotics used to treat CNS infections, relatively few studies have reported the use of intraventricular gentamicin.[6,18] Also, only a few studies have evaluated the therapeutic drug levels in CSF and serum.[19] These two findings underscore the significance of our case report. The goals of intraventricular antibiotic treatment include achieving the desired CSF concentrations at least 10–20-fold higher than the MIC of the pathogen, improving clinical symptoms, and resulting in negative CSF cultures.[1] However, the optimal timing of intraventricular antibiotic initiation is not well known, thus leading to a different threshold between institutions. Infrequent monitoring of CSF concentration

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highlights some limitations associated with the pharmacokinetics of intraventricular drug administration.[10,20] The duration of antibiotic treatment for CSF shunt infections is not clearly defined, and there are no controlled studies investigating different durations of antimicrobial treatment.[4]

Furthermore, a ratio of area under the curve over 24 hours to MIC (AUC/MIC) rather than serum trough concentrations might have been used in adjusting the appropriate vancomycin dosage.

In summary, we report two cases in which intraventricular antibiotics were used with systemic antibiotics to achieve clinical improvement in the treatment of ventriculitis. We maintained negative bacterial cultures of the CSF. Clinicians should closely monitor patients for possible adverse effects during the practice. Further pharmacokinetic data, clinical trials and standardized protocols or intraventricular antimicrobial therapy are crucial in filling the therapeutic gap and improving the quality of our practice.

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요약

뇌실염은 일반적으로 정맥 내 항생제를 통하여 치료하나, 불응성 뇌실염의 치료는 정맥 내 항생제 치료와 뇌실 내 항생제 치료의 병행이 요구되기도 한다. 이론적으로 항생제의 뇌실 내 투여는 정맥 내 단독 투여보다 뇌척수액에서 더 높은 항생제 농도에 도달할 수 있게 한다. 본 증례 보고는 기존의 전신 항생제 치료에 불응하는 폐렴 간균과 메티실린 내성 표피 포도상 구균에 각각 뇌실 내 겐타마이신과 반코마이신 투여를 통하여 뇌실염을 치료한 2례로서 이후에도 주요 합병증 등이 없어 이를 보고하는 바이다.