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CASE REPORT

Management of Multidrug-Resistant Gram-Negative Meningitis in Post-Operative Neurosurgical Patients: A Case Series

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ABSTRACT

Bacterial meningitis is a serious complication following neurosurgical procedures, particularly when foreign materials such as external ventricular drains, lumbar drains, or ventriculo-peritoneal shunts are used. In recent years, there has been an increase in cases caused by multidrug resistant *Acinetobacter baumannii*. We retrospectively reviewed cases from January 2022 to January 2024 at our institute and identified three cases of Acinetobacter meningitis amongst other gram-negative meningitis that occurred post neurosurgical procedures in which we had given antibiotics through intrathecal/intraventricular route along with intravenous route. One patient had undergone trans-nasal trans-sphenoidal endoscopic resection of pituitary tumour and the other two patients had decompressive craniectomy for brain hemorrhage. All patients were initially treated with intravenous polymyxins and other antibiotics. Due to limited response, intrathecal and intraventricular routes were employed for antibiotic administration which resulted in successful cerebrospinal fluid sterilization. Amongst three patients, two patients improved and one succumbed to complications. Our experience suggests that intrathecal or intraventricular administration of colistin can be used in managing multidrug resistant *Acinetobacter baumannii* meningitis which gets refractory to intravenous antibiotics.

Keywords: *Acinetobacter baumannii meningitis, intrathecal antibiotics, multi-drug resistance, post-operative neurosurgical patient.*

INTRODUCTION

Gram-negative meningitis has been increasing in recent times. Antibiotic resistance has become a global health threat, especially when organisms acquire resistance through various mechanisms.[1] In 2019, there were an estimated 236,000 deaths and 2.51 million incident cases due to meningitis globally. Global meningitis cases have reduced over time but remain high in some countries and regions. There are about 83% of meningitis cases worldwide that occur in low or lower-middle income countries. In contrast to gram positive meningitis, which is supported by well-defined epidemiological patterns and established treatment guidelines, gram negative meningitis poses substantial clinical challenges owing to its diverse etiological spectrum, heterogenous resistance mechanisms and restricted therapeutic armamentarium. Drug resistance to gram negative meningitis is shown with nearly all antibiotics, and this makes the treatment very challenging.[2] Mortality from this infection is seen to exceed 15%.[3]

In this case series, we have emphasized the early use of intrathecal and intraventricular route of antibiotic administration especially in those patients who are not showing any response to intravenous route alone. The shorter the time period of cerebrospinal fluid sterilization, the faster is the recovery time.[4] With increasing incidence of gram-negative meningitis that show sensitivity only to one or two available antibiotics, the treatment of these cases becomes extremely challenging. When treatment with limited antibiotics fail, then other routes of drug administration are used to penetrate the cerebrospinal fluid barrier. This decision should be made before the patient starts deteriorating due to the disease itself and the systemic side effects of the antibiotics.

In our retrospective analysis of post-surgical patients in the Intensive Care Unit (ICU), we came across three cases of gram-negative meningitis.

CASE 1

We report a case of a 48-year-old female who underwent trans-nasal trans-sphenoidal excision of pituitary macroadenoma in which lumbar drain was inserted and removed after 2 days. The patient was discharged followed by readmission with holo-cranial headache, vomiting and fever (101˚F). Glasgow Coma Scale (GCS) was E3 V4 M6. The patient had hypothyroidism with no other comorbidities. Cerebrospinal fluid (CSF) analysis showed proteins- 156, glucose- 2, and total count- 7,040 (neutrophils -70, lymphocytes- 14). Initially, Meropenem 2 grams 8 hourly, Colistin 4.5 MIU (million international units) 12 hourly and Vancomycin 500 milligram 6 hourly were started in view of gram negative cocci in CSF gram stain report. Colistin was started at an early stage as we suspected a possible nosocomial infection from adjacent ICU patient whose tracheal culture sensitivity report showed *Acinetobacter baumannii* sensitive to only colistin and resistant to all other antibiotics. After 2 days, antibiotics were switched from meropenem and vancomycin to minocycline (100 milligram 12 hourly) and injection colistin was continued for treatment. On the third day, the cerebrospinal fluid culture report showed *Acinetobacter baumannii*, which showed antibiotic sensitivity (intermediate) only to colistin.

By day 7, as patient was not improving much with intravenous antibiotics, we decided to give intrathecal colistin 0.125 MIU (million international units) along with intravenous antibiotics. Intravenous colistin was given for 23 days and minocycline for 13 days. Gradually, the patient's symptoms improved, and comprehension got better. A total of 10 doses of intrathecal colistin were given on alternate days by lumbar puncture. Although Infectious Disease Society of America (IDSA) recommends daily dosing of colistin, but we opted to give colistin on alternate days due to its narrow therapeutic index and lesser risk of neurotoxicity when spacing was done between doses. Colistin's therapeutic CSF concentration persist for more than 24-48 hours and daily dosing can therefore lead to drug accumulation without added benefit.[5] Cerebrospinal fluid culture became sterile after 11 days of starting intrathecal antibiotics. Cerebrospinal fluid study became normal after one month. The patient continued to have Glasgow coma scale of E3V5M6 with delayed response time. Later, the fever settled, and antibiotics were de-escalated gradually. She started accepting orally and was discharged with GCS 15 on day 44.

CASE 2

A 46-year-old male presented with altered mental status along with multiple episodes of vomiting. GCS was E1V2M4, and a bilateral cerebellar bleed was seen on Computed Tomography (CT) scan. Suboccipital craniectomy with Ommaya chamber placement was done. Later, tracheostomy was done, and weaning from the ventilator ensued. The patient worsened with fever and tachypnea. Tracheostomy cultures showed *Acinetobacter baumannii*, which showed sensitivity to antibiotics tigecycline and colistin (intermediate sensitivity). The patient was started on colistin 4.5 million international units 12 hourly, tigecycline 50 milligram 12 hourly and linezolid 600 milligram 12 hourly (in view of pus at the local site). After 14 days tigecycline was stopped and after 10 days, linezolid was stopped and was replaced by meropenem 2 gram 8 hourly and teicoplanin 400 milligrams for 3 doses followed by once a day.

On day 20th, CSF analysis was done, which showed 545 cells (neutrophils 81, lymphocytes 19, RBCs 20), proteins 53.7 g/dL, and glucose 33.9 mg/dL. Culture reports confirmed growth of *Acinetobacter baumannii*, which only had sensitivity (intermediate) to colistin. Inj teicoplanin was stopped and colistin (27 days) and meropenem (12 days) were continued. As recovery was taking time, 0.125 million international units (MIU) of colistin along with 5 milligrams of tigecycline were given via the Ommaya reservoir. Five doses of Colistin

and three doses of tigecycline were given on alternate days. Tigecycline has long CSF and tissue half-life with large volume of distribution and slow CSF clearance. Hence for the same reasons as colistin (to avoid drug accumulation which can cause neurotoxicity) we opted to administer tigecycline on alternate days. CSF culture came out to be sterile on day 14 after initiating treatment. The patient improved with GCS E4VttM6 but had difficulty in weaning from the ventilator. He was shifted to another hospital on bilevel positive airway pressure (BIPAP) support by day 38 due to financial reasons.

CASE 3

A 43-year-old male came to the emergency room with a right cerebellar infarct for which thrombolysis was done with tenecteplase 20 milligrams (0.2 mg/kg). During thrombolysis, blood pressure dropped, and CT showed hemorrhagic transformation of the infarct. He was intubated in view of low GCS (E1V1M5). Ommaya was placed on 2nd day and connected to external drainage system, and decompressive craniectomy was done on 5th day due to increase in bleed and increase in midline shift. Two weeks later, he developed ventilator-associated pneumonia (VAP) with *Acinetobacter baumannii* and was started on intravenous polymyxin B 5 lakh od and meropenem 500 mg 8 hourly (renal adjustment of doses were done).

On the 17th day, the CSF study showed cells – 1920 (N-88, L-8), proteins- 114, and glucose 43.2. On the 20th day, CSF culture showed Enterococcus faecium, which was sensitive to teicoplanin, vancomycin and gentamycin. Repeat CSF culture revealed Klebsiella pneumoniae showing intermediate sensitivity to colistin.

Intrathecal colistin 0.125 MIU was started on the 27th day. IV colistin was given for 24 days. Intrathecal colistin was given continuously for six days daily and then on alternate days for seven doses (a total of 13). Patient remained dull with the GCS varying between E1VttM1 and E2VttM2. His illness was complicated with acute kidney injury requiring dialysis, bed sores, hyperglycemia, CSF leakage from the surgical site, dyselectrolytemia and sepsis. He underwent cardiac arrest and was declared dead after about 71 days of his hospital admission.

DISCUSSION

Nosocomial meningitis is an uncommon cause of meningitis.[6] Risk factors for post-surgical meningitis include cerebrospinal leakage, prolonged placement of external hardware, and critically illness.[1,7] Treatment is challenging due to the low meningeal diffusion of antibiotics.[8] IDSA guidelines for post-neurosurgical meningitis therapy recommend ceftazidime or cefepime along with vancomycin as empirical coverage against gram-negative pathogens.[3] Frequently, gram-negative organisms such as *Acinetobacter baumannii* are shown to become resistant to cephalosporins and carbapenems.[2] In this situation, the role of Polymyxins appears to be promising. The duration of antibiotic therapy for gram-negative meningitis is described for 21 days.[9,10] Higher CSF/serum colistin drug concentrations were obtained when the drug was given via intraventricular or intrathecal route as the drug bypasses the blood brain barrier. Intrathecal administration of these antibiotics improves penetration to where the pathogen is located and therefore its activity, which can improve the cure rate and decrease mortality. Also, it has less systemic side effects when given via intrathecally or intraventricularly. The recommended dose of colistin by the intraventricular route is 10 mg (0.125 MIU) daily.[9] The most common side effect of using colistin is nephrotoxicity and neurotoxicity.[11] Use of tigecycline in nosocomial meningitis and encephalitis has also been on rise as positive outcomes have been seen with its use.[12] Moon et al[13] concluded that in 55% of the cases with colistin regimens in intrathecal or intraventricular administration of antibiotics and combined IV therapy, significant results were obtained in terms of cure, likewise, Bonis et al[14] concluded that intra-ventricular therapy in addition to intravenous therapy allows for favorable results in curing patients.

In our first case, the cause of meningitis is thought to be the lumbar drain placement. Cross-infection could have occurred from an adjacent bed in the ICU (as was evident from the similar culture sensitivity reports of tracheal culture of adjacent patient). In our second case, the lungs were likely the source of infection, as gram-negative bacillus could have travelled via the hematogenous route from the lungs to the brain. In our third case, Ommaya placement and prolonged ventilator requirement with low immunity levels could have added to the risk of developing gram-negative meningitis.

Antibiotic resistance is an immediate threat, especially in critically ill patients. Our goal was to firstly minimize antibiotic resistance by rational usage. Secondly, we explored alternate routes of administration of drugs besides the intravenous route. Use of external hardware in neurosurgical procedures should be limited to minimal days and stringent infection control measures should be taken while handling this hardware. Cross infection should be minimized in ICU with use of stringent hand washing, wearing gloves while touching bedside of the patient and likewise infection control measures.

CONCLUSION

Gram-negative meningitis, particularly following neurosurgical procedures, is associated with high morbidity and mortality due to increased multidrug resistance. Early adjunctive intrathecal or intraventricular antibiotic therapy, in addition to intravenous treatment, may improve outcomes.

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