

Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of tigecycline for post-neurosurgical intracranial infections due to MDR/XDR *Acinetobacter baumannii*: A retrospective cohort study

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Abstract. Intracranial infection is a complication of neurosurgery that can lead to severe neurological complications, greatly increasing the risk of mortality. Intracranial infection caused by multidrug-resistant *Acinetobacter baumannii* (MDR-AB) is one of the most severe complications of craniotomy. However, the availability of effective therapeutic options for such infections remains limited. Therefore, the present study aimed to assess the therapeutic efficacy of intrathecal/intracerebral (ITC) ventricle tigecycline injection for managing post-neurosurgical intracranial infections caused by MDR-AB. The present retrospective study was conducted from January 2014 to December 2023 at the Second Affiliated Hospital of Shandong First Medical University (Taian, China), which included 15 cases of MDR-AB positivity in the cerebrospinal fluid (CSF) cultures after neurosurgery. Patients treated with intravenous and intrathecal/ITC tigecycline ventricle injection were assigned to the 'ITV + ITC' group, whereas patients treated without intrathecal/ITC injection were assigned to the 'ITV' group. Data for general information, treatment history, the results of biochemical indicators in CSF and the microbiological clearance rate were collected and analyzed. No significant differences were observed in characteristics, susceptibility testing or empirical antimicrobial use between

the two groups after treatment. However, after treatment, the ITV + ITC group exhibited a significantly decreased body temperature, whilst the biochemical indicators present in CSF were significantly improved. In addition, the ITV + ITC group had a significantly higher microbiological clearance rate (5/6; 83.33%) compared with that in the ITV group (2/9; 22.22%). These findings suggest that intravenous plus intrathecal/ITC ventricle injection of tigecycline is an effective regimen for treating intracranial infections caused by MDR-AB.

Introduction

Intracranial infection poses a significant risk following craniotomy, representing one of the most severe complications (1). External trauma, neurosurgical operations, cerebrospinal fluid (CSF) leakage and the presence of external devices constitute a number of potential risk factors for bacterial infiltration into the CSF (2). There is a growing reported incidence of intracranial infections caused by *Acinetobacter baumannii*, with its contribution to the overall incidence rate of bacterial meningitis ranging from 3.6-11.2% (3). Overall, the mortality rate from *Acinetobacter baumannii* infection worldwide ranges from 15.0 to 71.5% (4,5). *Acinetobacter baumannii* is a non-fermenting gram-negative bacterium that is one of the most important members of the *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. group of microorganisms. It is a well-known hospital pathogen that poses a serious threat to public health, especially to patients in intensive care units (6-9). Due to multiple factors, such as the irrational use of antibiotics, cross-infection among inpatients and the transmission of resistance genetic elements, an increasing number of strains of *Acinetobacter baumannii* have evolved into multidrug resistant (MDR), extensive drug resistant (XDR) and even pan-drug resistant strains (10), which limits the clinical treatment options of antibiotics. At present, carbapenems are frequently utilized for treating *Acinetobacter baumannii*. However, there have been numerous

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reports of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in recent years (11,12). Given the high mortality and resistance rates, prompt treatment of brain infections caused by MDR/XDR *Acinetobacter baumannii* is imperative. The primary therapeutic methods for such conditions include polymyxin B and tigecycline (13-16).

According to the International Consensus Guidelines for the Optimal Use of the Polymyxins, colistin methanesulfonate (CMS) is the recommended choice for intraventricular or intrathecal injection for treating brain infections caused by MDR/XDR-*Acinetobacter baumannii* (Ab) (17). However, the acquisition of CMS was challenging and relatively costly in second- and third-tier cities in China a few years ago. Therefore, polymyxin B is commonly used in clinical practice for intraventricular or intrathecal injection. However, polymyxin B can cause neurotoxicity. Following the intraventricular administration of polymyxin B, patients may experience symptoms resembling meningitis, such as fever, headache, stiff neck, elevated CSF cell count and protein content (18). The aforementioned symptoms resemble those of intracranial infections, potentially impacting the assessment of treatment efficacy. According to the latest advancements for the treatment of intracranial infections, tigecycline has emerged as the preferred choice for clinical application (19-21). Due to the limitations of the blood-brain barrier, coupled with the increasing resistance of bacteria to antibiotics, the ability of different antibiotics to enter the CSF also varies, which limits the options for treating *Acinetobacter* infections in the brain. Therefore, the sole administration of intravenous antibiotics is not likely to be an efficacious approach for treating brain infections. There have been studies reporting that combining intravenous (ITV) injection with intracerebral (ITC) injection can enhance the concentration of the drug in the CSF (13,14). Tigecycline demonstrates potent antibacterial activity against both gram-negative and gram-positive bacteria, which is consistent with the synergistic effects of a number of antimicrobial drugs. However, ITV tigecycline is not recommended for the treatment of intracranial infections due to its limited ability to penetrate the blood-brain barrier (22,23). In previous years, studies have been performed assessing the use of tigecycline intraventricular injection for the treatment of intracranial infections (19-21). However, they are mostly individual case analyses. Therefore, to validate the efficacy of this treatment and bolster the evidence base, a retrospective analysis of the impact of ITV antibiotics alone compared with combined ITV and ITC tigecycline injection in 15 patients with MDR/XDR-Ab intracranial infections following neurosurgery was conducted. To the best of the authors' knowledge, the present study represents the largest cohort investigation to date regarding the efficacy of ITV and ITC administration of tigecycline for treating MDR/XDR-Ab intracranial infections in patients who underwent neurosurgery.

Patients and methods

Screening of patients. The present study was a retrospective cohort analysis conducted at the Second Affiliated Hospital of Shandong First Medical University (Taian, China) spanning from January 2014 to December 2023. Consecutive adult patients (aged >18 years) with a diagnosis of intracranial

infection due to MDR/XDR-Ab after a neurosurgery were recruited without any prior screening of the participants. The exclusion criteria were as follows: i) Polymicrobial results from CSF culture; ii) infections not caused by MDR/XDR-Ab; iii) no complications occurring after neurosurgery; or iv) there was intracranial colonization due to MDR/XDR-Ab. The patient selection process is outlined in Fig. 1. The present study was approved (approval no. 2023-H-007; Taian, China) by the Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University and all patients or their families signed the informed consent.

Patient samples for which CSF cultures were positive for multidrug-resistant *Acinetobacter baumannii* (MDR-AB) were collected after a neurosurgery at the Second Affiliated Hospital of Shandong First Medical University (Taian, China) from 2014 to 2023. Simple cases of MDR-AB infection after neurosurgery were rare. There were only 15 cases consistent with MDR-AB infection after cranial surgery with complete data, of whom 9 received only ITV treatment as the 'ITV' group, whilst the remaining 6 received ITV treatment combined with ITC treatment, who were designated into the 'ITV + ITC' group.

The criteria for diagnosing MDR/XDR-Ab intracranial infections following neurosurgical procedures are outlined as follows (13,14): i) CSF culture is positive, with MDR defined as resistance to at least three antibiotics whereas XDR was defined as resistance to all but one or two antibiotics (15); ii) a minimum of two symptoms (a fever >38°C, headache, signs of meningitis or indications related to cranial nerves) must be observed, with no alternative explanation; and iii) CSF glucose level <2.4 mmol/l, CSF nucleated cells >8x10⁶/l or protein level in the CSF >0.6 g/l. A positive CSF culture is classified as colonization or contamination if the patient exhibits no clinical symptoms and the levels of glucose, nucleated cells and protein in the CSF are found to be within normal ranges (14).

Treatment protocol. In the ITV + ITC group, patients received tigecycline (Nanjing Haichen Pharmaceutical Co., Ltd.) through ITV injection and ITC injection. The ITV dose was 100 mg every 12 h and 5 mg of tigecycline was administered through a lumbar puncture or CSF drainage catheter twice daily. After ITC injection of tigecycline, the CSF drainage tube was temporarily closed for 4 h. Patients in the ITV group exclusively received antibiotic therapy through the ITV route without ITC injection (24,25).

Collection of epidemiological characteristics. The data from cases meeting the present study criteria were collected from computer and electronic medical records (Second Affiliated Hospital of Shandong First Medical University, Taian, China). Epidemiological features encompassing age, sex, underlying diseases, co-morbidities, surgical procedures, co-infections, Glasgow Coma Scale (GCS) scores and temperature were recorded. The GCS was introduced in 1974 by Teasdale and Jennet to evaluate consciousness levels and brain activity in patients undergoing neurosurgery. This scale consists of the following three primary components: i) Eye opening; ii) verbal response; and iii) motor skills. Each component receives a score based on the patient's reactions, culminating in a total score that can reach up to 15 points (26,27).

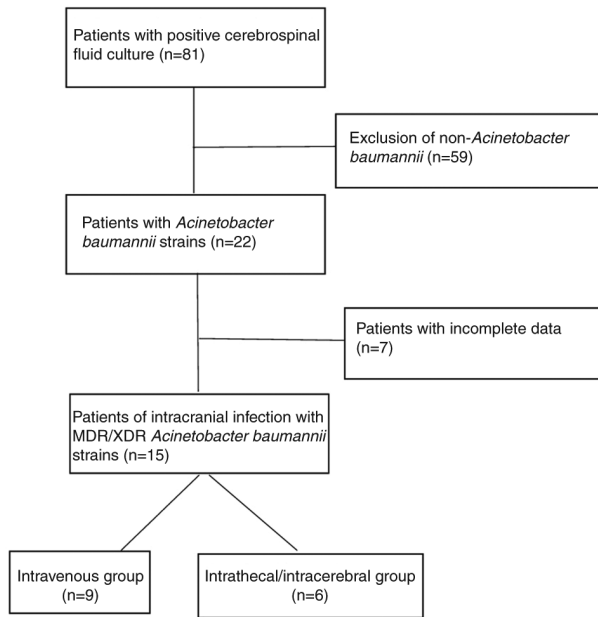


Figure 1. Flowchart of study participant enrollment.

Antimicrobial susceptibility tests. The results of the antimicrobial susceptibility tests for the isolated *Acinetobacter baumannii* and the initial empiric antimicrobial therapy were recorded. The Second Affiliated Hospital of Shandong First Medical University adopts the BD Phoenix™ 100 bacterial identification drug sensitivity analyzer (BD Biosciences). According to the microbroth dilution method recommended by the Clinical and Laboratory Standards Institute in 2019 (28), the minimum inhibitory concentration (MIC) of *Acinetobacter baumannii* was determined against nine antibacterial drugs. According to the multiple dilution method, a series of antimicrobial solutions with decreasing concentration gradient was obtained in each row of the 96-well plate. A volume of 100 µl/well bacterial suspension with 5x10⁵ colony-forming unit (CFU)/ml prepared in cation-adjusted Mueller-Hinton broth (CaMHB; BD Biosciences) was inoculated in 96-well plates. In addition, a positive control (only bacterial liquid) and a negative control (only CaMHB) were added. After the sample was added, the plate was incubated at 37°C for 16-20 h. The MIC was defined as the lowest concentration of antibiotic giving complete inhibition of visible growth. The MIC of amikacin, tigecycline, carbapenems (imipenem, meropenem), cephalosporins (cefazolin, ceftazidime, cefotaxime, cefepime), and polymyxin B were measured.

Biochemical indicators and microbiological clearance rate. The effectiveness of the treatment was evaluated based on the aforementioned clinical and microbiological parameters. Clinical efficiency was defined as either the resolution or improvement of symptoms. The microbiological efficacy was characterized by the eradication or clearance of *Acinetobacter baumannii* in CSF samples following treatment, which was confirmed by three consecutive CSF cultures (24). The overall effectiveness of the treatment was determined by integrating clinical efficacy, microbiological clearance rates

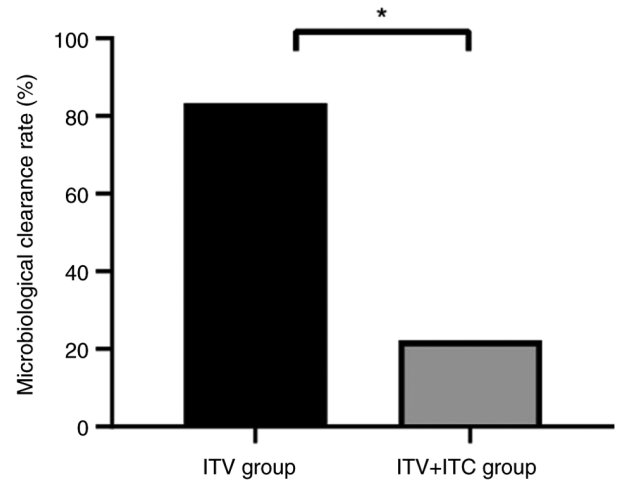


Figure 2. Microbiological clearance rate (%) between the two groups after treatment. *P<0.05.

and biochemical indicators [polymorph nuclear neutrophils (PMNs), chlorine, glucose, and protein levels] present in the CSF.

Statistical analysis. Statistical analyses were conducted using the SPSS 17.0 (SPSS, Inc.) software system. Categorical data are presented as [n, (%)] and compared between the two groups utilizing the Mann-Whitney U test. Continuous data were analyzed for differences between groups using Student's t-test. A two-tailed P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic characteristics of study participants. In 81 cases of positive CSF culture, 22 patients were found to be infected with *Acinetobacter baumannii* (n=22; 27.16%). After excluding cases with incomplete data, a total of 15 neuro-surgical postoperative MDR/XDR-Ab intracranial infection cases were ultimately incorporated into the present study. There were 9 cases in the ITV group and 6 cases in the ITV + ITC group. The baseline characteristics of patients in the two groups, revealing no significant differences in sex, age, primary disease, surgeries underwent, GCS scores or fever, are presented in Table I.

Susceptibility testing and antimicrobial therapies. A comprehensive overview of the antibiotic resistance profiles observed in the 15 patients is presented in Table II. Among the antibiotics assessed, MDR/XDR-Ab exhibited complete resistance to carbapenems and cephalosporins (with a resistance rate of 100%), whilst demonstrating resistance rates of 0.00 and 6.67% to polymyxins and tigecycline, respectively. The antibiotic resistance detection results exhibited no statistically significant differences between the two groups.

In Table III, it was revealed that the most frequently utilized antibiotic combination in the ITV group was tigecycline + meropenem (33.33%). By contrast, in the ITV + ITC group, the most commonly used combination was tigecycline + cefoperazone-sulbactam (50.00%). There was no statistically

Table I. Baseline characteristics of patients enrolled in the study.

Characteristics	ITV group (n=9)	ITV + ITC group (n=6)	P-value
Sex (male), n (%)	8 (88.89%)	5 (83.33%)	0.864
Age (years)	50.22±14.31	44.33±11.02	0.4106
Primary disease, n (%)			0.529
Cerebral hemorrhage	3 (33.33%)	3 (50.00%)	
Craniocerebral trauma	5 (55.56%)	3 (50.00%)	
Benign intracranial tumor	1 (11.11%)	0 (0.00%)	
Comorbidities, n (%)			0.456
Diabetes	2 (22.22%)	0 (0.00%)	
Hypertensive disease	2 (22.22%)	1 (16.67%)	
Surgeries, n (%)			0.851
Craniotomy evacuation of hematoma and decompressive craniectomy	4 (44.44%)	3 (50.00%)	
Intracranial tumor resection	1 (11.11%)	0 (0.00%)	
Craniotomy aneurysm clipping	0 (0.00%)	1 (16.67%)	
Drainage of intracranial hematoma	2 (22.22%)	2 (33.33%)	
Ventricle peritoneal shunt	1 (11.11%)	0 (0.00%)	
Lumbar cistern drainage	9 (100.00%)	5 (83.33%)	
Ommaya reservoir	1 (11.11%)	1 (16.67%)	
Coinfection, n (%)			
Lung	5 (55.56%)	3 (50.00%)	0.864
GCS score	6.86±3.39	7.20±3.11	0.862
Fever (°C)	38.30±0.88	38.82±0.49	0.217

Table II. Susceptibility testing results for isolated *Acinetobacter baumannii*.

Antibiotics	MIC breakpoint (mg/l)	Total (n=15)	ITV group (n=9)	ITV + ITC group (n=6)	P-value
Antibiotic resistance, n (%)					0.888
Amikacin	R≥32	13 (86.6%)	7 (77.78%)	6 (100%)	
Tigecycline	R≥8	1 (6.67%)	1 (11.11%)	0 (0%)	
Carbapenems					
Imipenem	R≥8	15 (100%)	9 (100%)	6 (100%)	
Meropenem	R≥8	15 (100%)	9 (100%)	6 (100%)	
Cephalosporins					
Cefazolin	R≥16	15 (100%)	9 (100%)	6 (100%)	
Ceftazidime	R≥16	15 (100%)	9 (100%)	6 (100%)	
Cefotaxime	R≥32	15 (100%)	9 (100%)	6 (100%)	
Cefepime	R≥16	15 (100%)	9 (100%)	6 (100%)	
Polymyxin B	R≤0.5	0 (0%)	0 (0%)	0 (0%)	

significant difference in the empirical antimicrobial therapy applied between the two groups (Table III).

Microbiological clearance, biochemical indicators in CSF, white blood cell (WBC) and body temperature. As demonstrated in Fig. 2, the ITV + ITC group demonstrated a significantly higher microbiological clearance rate (5/6; 83.33%) compared with that in the ITV group (2/9; 22.22%).

Prior to treatment, the WBC count was markedly elevated in the ITV + ITC group compared with that in the ITV group. Nevertheless, no significant differences were observed in the PMNs, chlorine, glucose, protein levels in CSF or body temperature between the two groups (Fig. 3).

After treatment, the ITV + ITC group exhibited a significantly lower body temperature compared with that in the ITV group (37.62±0.81°C vs. 36.75±0.42°C), a significantly

Table III. Initially applied empirical antimicrobial therapies.

Antibiotics, n (%)	ITV group (n=9)	ITV + ITC group (n=6)	P-value
Tigecycline + ceftazidime-avibactam	1 (11.11%)	3 (50.00%)	0.113
Tigecycline + meropenem	3 (33.33%)	1 (16.67%)	
Tigecycline + ceftazidime-avibactam + meropenem	1 (11.11%)	2 (33.33%)	
Meropenem + ceftazidime-avibactam	2 (22.22%)	0 (0.00%)	
Ceftriaxone + ceftazidime-avibactam	1 (11.11%)	0 (0.00%)	
Meropenem + vancomycin	1 (11.11%)	0 (0.00%)	

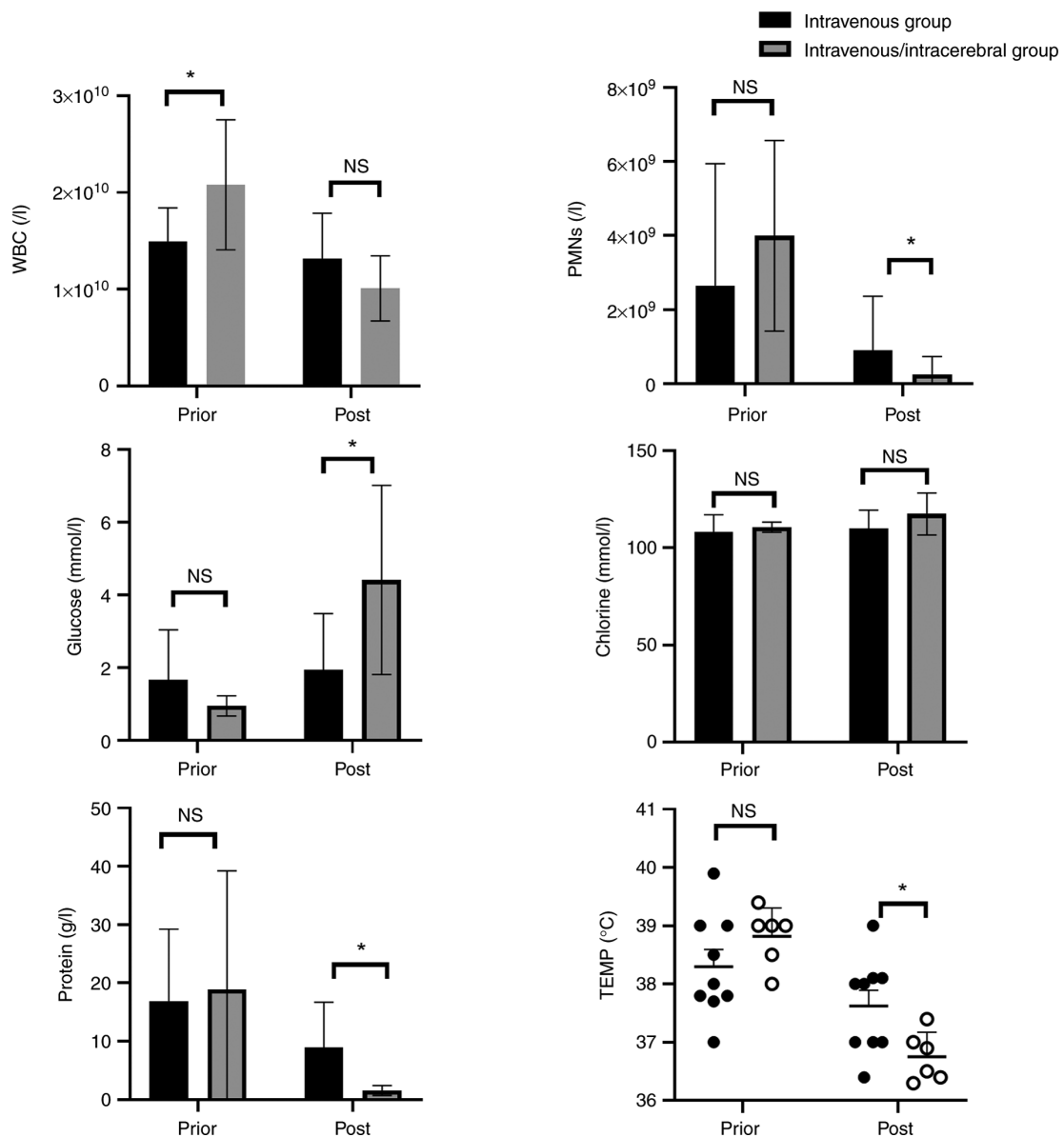


Figure 3. Biochemical indicators and body temperature before and after treatment in the two groups. *P<0.05. WBC, white blood cell; PMNs, polymorph nuclear neutrophils; NS, not significant.

reduced number of PMNs in the CSF ($1,268.8 \pm 1,538.3$ vs. $79.8 \pm 135.6 \times 10^6/l$), a significantly superior recovery of the glucose levels in the CSF (1.943 ± 1.543 mmol/l vs. 4.413 ± 2.60 mmol/l) and significantly reduced levels of

total protein in the CSF (7.76 ± 8.54 g/l vs. 1.545 ± 0.854 g/l). However, no statistically significant differences were observed in WBC level or in the chlorine level in the CSF between the two groups.

Discussion

Acinetobacter baumannii is a significant pathogen that can cause serious hospital-acquired infections and is considered to be one of the most perilous gram-negative bacteria species (29,30). *Acinetobacter baumannii* is capable of causing healthcare-associated infections, including ventilator-associated pneumonia, sepsis, urinary tract infections, meningitis and surgical site infections (29,30), which may result in elevated mortality rates among affected patients. The risk factors associated with these infections can encompass mechanical ventilation, the administration of broad-spectrum antibiotics, ICU length of stay and coma (31). According to statistics, ~1 million individuals worldwide contract infections caused by *Acinetobacter baumannii* each year, with 50% of such cases attributed to MDR (32). The mortality rate for ICU-acquired *Acinetobacter baumannii* infections ranges from 45 to 60%, but can even reach 84.3% in the case of XDR strains (33,34). According to the World Health Organization's list of antibiotic-resistant bacteria released in 2017, CRAB were identified as the bacteria posing the greatest threat to human health and being most in need of related antibiotic development (35). In addition, *Acinetobacter baumannii* is an important pathogen that can cause central nervous system (CNS) infections, resulting in a mortality rate ranging from 15 to 71% for *Acinetobacter* meningitis (36). The occurrence of CNS infections caused by MDR *Acinetobacter baumannii* presents a significant challenge to neurosurgical patients.

Acinetobacter baumannii is a Gram-negative opportunistic pathogen that has emerged as one of the most alarming hospital-acquired infection pathogens over the last decade (29,37). The majority of strains also demonstrate MDR, where the majority of the globally prevalent major clades are only susceptible to polymyxin and tigecycline (38,39). Tigecycline and polymyxins are typically reserved as the last resort options for treating infections caused by carbapenem-resistant bacteria (38,39). Furthermore, polymyxins are difficult to purchase and are typically too expensive for certain patients. For these reasons, tigecycline is often preferred as a treatment option for CNS infections.

Tigecycline belongs to a relatively novel category of antibiotics known as 'glycylcyclines' (40), which demonstrate efficacy against strains resistant to *Acinetobacter baumannii* (41). Pallotto *et al* (42) previously found difficulty in delivering tigecycline into the CSF of a patient with a ventriculoperitoneal shunt infection, where the concentration of tigecycline in the CSF was found to be ~7.9% that found in the serum. Despite the reported observations in which *in vitro* sensitivity tests have indicated that tigecycline is effective against CNS infections, the expected therapeutic outcomes in actual clinical practice have remained elusive likely for this reason. Previously, in a study by Abdallah *et al* (25), the addition of IVT tigecycline successfully eradicated the MDR *Acinetobacter baumannii* from the CSF, where the signs of infection disappeared. Additionally, direct intrathecal/IVT injection of tigecycline could enhance its concentration within the CNS. In addition, Long *et al* (43) reported that 8 patients with MDR

Acinetobacter baumannii meningitis/ventriculitis who were treated with ITC and/or ITV tigecycline demonstrated favorable clinical efficacy without any associated complications. Although numerous studies have reported that intracranial injection of tigecycline significantly improved symptoms of meningitis caused by MDR/XDR-Ab (18,25,43), these studies are mostly case reports, where no statistical analysis was conducted between the groups of ITV and ITC injection of tigecycline. In the present study, medical records were collected, which were classified, grouped and statistically compared. Specifically, the intracranial injection group and the non-intracranial injection group were compared, which confirmed that the combination of ITV and intrathecal/intracranial injection of tigecycline is superior to conventional ITV antibiotic therapy for treating cerebral infections caused by MDR/XDR-Ab.

It must be noted that the intracranial administration of tigecycline is still considered to be an off-label method, where there is currently no universally accepted standard for its dosage and frequency of administration (18). Due to the limited availability of large-scale studies, there may be inherent biases in assessing its efficacy and safety. In the present study, the intracranial dose of tigecycline used was 5 mg twice daily. Compared with the ITV group, the ITV + ITC group exhibited a significant improvement in the clinical efficacy, where no adverse reactions were observed. The results were consistent with recommended dose from Huang *et al* (18).

The present study has several limitations. It is not a formal treatment trial, but rather a retrospective analysis of previous treatment regimens for MDR/XDR-Ab-induced intracranial infections. There was a lack of pharmacokinetic data analysis and a lack of monitoring of tigecycline concentration in the blood and CSF. The optimal intrathecal dose of tigecycline still requires verification and discussion in more trials. Additional multicenter randomized controlled trials are required to confirm the efficacy and safety of this strategy. In the future, data will be shared with other medical institutions to jointly study the treatment of intracranial MDR-AB infection. Nevertheless, the present results suggest that ITC and ITV administration of tigecycline is superior to ITV administration alone for the treatment of intracranial infections caused by MDR/XDR-Ab. In addition, to the best of the authors' knowledge, the present study is the largest cohort study to date on the efficacy of ITV and ITC administration of tigecycline for the treatment of MDR/XDR-Ab intracranial infections in patients who underwent neurosurgery.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RA, XT and XM designed the study. LG, GG and YL collected the data. XM and TZ analyzed and interpreted the patient general data. RA, XT and XM performed statistical analyses, wrote the manuscript and reviewed the literature. All authors read and approved the final version of the manuscript. XT and RA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved (approval no. 2023-H-007; Taian, China) by the Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University and all patients or their families signed the informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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