Intrathecal or intraventricular antimicrobial therapy for post-neurosurgical intracranial infection due to multidrug-resistant and extensively drug-resistant Gram-negative bacteria: A systematic review and meta-analysis

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A R T I C L E   I N F O

Article history:
Received 11 February 2019
Accepted 1 August 2019

Editor: Po-Ren Hsueh

Keywords:
Intrathecal
Intraventricular
Intracranial infection
Gram-negative bacteria
Multidrug-resistant
Extensively drug-resistant

A B S T R A C T

This review investigated the effectiveness and safety of intrathecal (ITH) or intraventricular (IVT) antimicrobial therapy for post-neurosurgical intracranial infection due to multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria. Electronic databases including PubMed, EMBASE and the Cochrane Library databases were searched for clinical studies that compared the addition of ITH/IVT therapy with intravenous (IV) monotherapy in the treatment of post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria. Eligible articles were analysed using Stata/SE software v.12.0. Publication bias was assessed using Begg’s funnel plot and Egger’s test. Nine studies involving 296 patients were included. The odds ratio (OR) for death (IV+ITH/IVT versus IV) reported in the included studies ranged from 0.02–0.93. The overall pooled OR was 0.15 [95% confidence interval (CI) 0.08–0.28; \( P < 0.001 \)] and the risk of mortality was significantly different between the two groups. Microbiological clearance was significantly different between the two groups, with a pooled OR of 0.02 (95% CI 0.01–0.10; \( P < 0.001 \)). In observational studies, addition of ITH/IVT antimicrobial therapy is associated with a lower risk of mortality and a higher microbiological clearance rate, with mild adverse effects, in patients with post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria. A well-designed randomised controlled trial is necessary to address this important issue.

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1. Introduction

Post-neurosurgical intracranial infection is one of the serious complications of neurosurgical procedures and is associated with significant morbidity and mortality [1–3]. Cerebrospinal fluid (CSF) shunts and drains, neurosurgery or head trauma, and intrathecal infusion pumps are associated with infection [4]. Staphylococci and resistant Gram-negative bacilli are the most likely aetiologi-cal agents [4,5]. The mortality rate is higher among patients with Gram-negative bacterial intracranial infection than among those with other pathogenic bacteria [6] and, even worse, treatment of the infection has become extremely difficult because of the increasing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates of Acinetobacter baumannii, Klebsiella pneumoniae and Pseudomonas aeruginosa [7]. Post-neurosurgical intracranial infection is an emergency and requires early diagnosis and treatment with appropriate antibiotics.

According to drug susceptibility analyses, there are only a few drugs, such as the polymyxins and aminoglycosides, that are effective against MDR/XDR Gram-negative bacteria. However, due to very low brain penetration, intracranial infection does not show any improvement when treated with these antimicrobial agents intravenously alone. Thus, intrathecal (ITH) or intraventricular (IVT) administration of antibiotics has been considered the last resort for MDR/XDR Gram-negative bacteria ventriculitis and meningitis not responding to intravenous (IV) regimens [8]. ITH/IVT administration can bypass the blood–brain barrier, achieve a more effective concentration of antibiotics in the CSF and reduce systemic side effects [9,10]. However, there is insufficient evidence to support ITH/IVT therapy and it is not approved by the US Food and Drug Administration (FDA). In addition, its potential neurotoxicity, such as chemical meningitis and ventriculitis, cannot be ignored, although these reactions have been reported to be mild and reversible [8,11–13]. Therefore, the aim of this systematic review and meta-analysis was to compare the mortality and microbiological...
clearance of the addition of ITH/IVT therapy with IV monotherapy in the treatment of post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria and to evaluate the safety of ITH/IVT administration.

2. Methods

2.1. Sources of information and search strategy

Relevant studies were identified by searching electronic databases including PubMed, EMBASE and the Cochrane Library up to 31 July 2018. References of each article selected were searched manually to identify additional potentially relevant studies. Conference abstracts were not searched for. No language restrictions were applied. The search terms used were 'intrathecal' or 'intraventricular', 'Gram-negative bacteria', 'intracranial infection' or 'central nervous system infection' or 'meningitis' or 'ventriculitis'.

2.2. Inclusion and exclusion criteria

The study inclusion criteria were: (i) study design: randomised controlled trial (RCT), prospective or retrospective study; (ii) study population: patients with post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria; (iii) studies that compared the effects of IV plus ITH/IVT administration therapy with IV monotherapy; and (iv) outcome of mortality reported by the study. Case reports or case series were excluded.

2.3. Data extraction and quality assessment

Two researchers independently reviewed the included studies and extracted relevant information from each study. Disagreement between the two reviewers was resolved by consensus. The following variables were extracted from each study if available: first author’s surname; publication year; study design; study setting; study period; type of infection; organism; demographic characteristics of the patients; ITH/IVT drug administration; microbiological clearance; mortality; and odds ratio (OR) with 95% confidence interval (CI) of outcomes. Study quality was assessed using the nine-star Newcastle–Ottawa Scale for assessing the quality of observational studies in meta-analyses (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

2.4. Statistical analysis

For each study, ORs with 95% CIs were retrieved to estimate outcomes. Heterogeneity of studies was assessed by $\chi^2$ test and the $I^2$ measure of inconsistency. A fixed-effects model was applied unless statistical heterogeneity was found ($P < 0.1$ or $I^2 > 50$%); otherwise, a random-effects model was used. Potential publication bias was assessed with Begg’s funnel plot and Egger precision weighted linear regression test. All statistical analyses were conducted using Stata Statistical Software: Release 12 (StataCorp LP, College Station, TX, USA).

3. Results

A total of 166 articles were retrieved; the process of identifying relevant studies is shown in Fig. 1. After reviewing titles and abstracts, 21 articles were identified as potentially eligible for inclusion. Among the 21 studies, 12 were excluded from further analysis for various reasons (3 studies were excluded because they did not involve MDR/XDR Gram-negative bacteria, 6 were excluded because they did not compare IV plus ITH/IVT with IV administration and 3 were excluded because they were case reports) (Fig. 1). Finally, nine retrospective studies involving 296 patients were included in the meta-analysis [11,14–21]. Four studies were conducted in Asia [11,17–19], another four in Europe [14–16,20] and
Table 1
Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author/publication year</th>
<th>Study design</th>
<th>Country</th>
<th>Study period</th>
<th>Type of infection</th>
<th>Organism</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Sex ratio (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fotakopoulos, 2016 [15]</td>
<td>Retrospective</td>
<td>Greece</td>
<td>2006–2014</td>
<td>Nosocomial meningitis/ventriculitis following neurosurgical intervention</td>
<td>MDR Gram-negative bacteria (A. baumannii, 70.5%)</td>
<td>34</td>
<td>50.6</td>
<td>0.62:1</td>
</tr>
<tr>
<td>Sipahi, 2018 [20]</td>
<td>Retrospective</td>
<td>Turkey, France</td>
<td>Jan. 2007–Apr. 2016</td>
<td>Nosocomial post-neurosurgical meningitis</td>
<td>MDR A. baumannii</td>
<td>15</td>
<td>49.5 ± 18.2</td>
<td>1.5:1</td>
</tr>
</tbody>
</table>

CR, carbapenem-resistant; XDR, extensively drug-resistant; MDR, multidrug-resistant.
* Data were expressed as the median.

Table 2
Administration of intrathecal or intraventricular (ITH/IVT) antibiotic therapy, outcomes and quality of the included studies

<table>
<thead>
<tr>
<th>Author/publication year</th>
<th>ITH/IVT administration</th>
<th>Microbiological clearance</th>
<th>Mortality</th>
<th>Death (n/N)</th>
<th>OR (95% CI) of outcome</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV+ITH/IVT</td>
<td>IV</td>
<td>IV+ITH/IVT</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chusri, 2018 [11]</td>
<td>Colistin (dosage regimen of 150 000–200 000 IU daily); the duration of consolidative IV treatment was 18 days</td>
<td>N/A</td>
<td>N/A</td>
<td>5/17</td>
<td>9/16</td>
<td>0.32 (0.08–1.36)</td>
</tr>
<tr>
<td>De Bonis, 2016 [14]</td>
<td>IVT colistin (10–20 mg/day); the median length of therapy was 26.5 days</td>
<td>9/9</td>
<td>3/9</td>
<td>3/9</td>
<td>7/9</td>
<td>0.14 (0.02–1.16)</td>
</tr>
<tr>
<td>Fotakopoulos, 2016 [15]</td>
<td>IVT colistimethate sodium (mean dose 170 000 ± 400 IU); the duration of treatment was 16.0 ± 8.3 days</td>
<td>N/A</td>
<td>N/A</td>
<td>3/23</td>
<td>8/11</td>
<td>0.06 (0.01–0.34)</td>
</tr>
<tr>
<td>Guardado, 2008 [16]</td>
<td>ITH therapy with colistin (8 cases) and aminoglycosides (9 cases)</td>
<td>N/A</td>
<td>N/A</td>
<td>2/17</td>
<td>11/20</td>
<td>0.22 (0.04–1.14)</td>
</tr>
<tr>
<td>Moon, 2013 [17]</td>
<td>ITH/IVT colistimethate (8 cases and aminoglycosides (2 cases)</td>
<td>N/A</td>
<td>N/A</td>
<td>2/10</td>
<td>11/12</td>
<td>0.02 (0.00–0.30)</td>
</tr>
<tr>
<td>Pan, 2019 [18]</td>
<td>ITH polymyxin B 50 000 IU/day</td>
<td>21/23</td>
<td>7/38</td>
<td>2/23</td>
<td>21/38</td>
<td>0.08 (0.02–0.38)</td>
</tr>
<tr>
<td>Shofty, 2016 [19]</td>
<td>10 with colistin (median dose 50000 IU/day) and 13 with amikacin (median dose 37.5 mg/day) for a total median duration of 9 days and 12 days, respectively</td>
<td>N/A</td>
<td>N/A</td>
<td>2/23</td>
<td>9/27</td>
<td>0.19 (0.04–1.00)</td>
</tr>
<tr>
<td>Sipahi, 2018 [20]</td>
<td>ITH colistin 2 × 5 mg (19 days, 20 days, 22 days)</td>
<td>N/A</td>
<td>N/A</td>
<td>1/3</td>
<td>6/12</td>
<td>0.50 (0.04–7.10)</td>
</tr>
<tr>
<td>Tuon, 2010 [21]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2/2</td>
<td>13/15</td>
<td>0.93 (0.03–25.68)</td>
</tr>
</tbody>
</table>

IV, intravenous; OR, odds ratio; CI, confidence interval; N/A, not available.

one in South America [21] (Table 1). According to the Newcastle–Ottawa Scale, one retrospective study was fair (score 5) and the remaining eight studies were rated as good or excellent quality (score range, 6–9) (Table 2).

The OR for death (IV+ITH/IVT versus IV) reported in the included studies ranged from 0.02–0.93 (Table 2). No significant heterogeneity (P = 0.51; I² = 0%) was observed across the nine included studies; thus, a fixed-effects model was used to analyse the studies (Fig. 2). The overall pooled OR was 0.15 (95% CI 0.08–0.28; P < 0.001) and the risk of mortality was significantly different between the two groups. Based on variable descriptions of microbiological clearance, only two studies were analysed. Microbiological
clearance was significantly different between the two groups, with a pooled OR of 0.02 (95% CI 0.01–0.10) without significant heterogeneity ($P = 0.88$, $I^2 = 0\%$) (Fig. 2). Only one study described side effects, showing no significant difference between the two groups [517 (29.4\%) vs. 616 (37.5\%); $P = 0.62$] [11]. Other studies had no serious adverse reactions observed or they were not described. Graphical inspection through Begg’s funnel plot (Fig. 3) and quantitative evaluation through Egger’s test ($P = 0.87$) did not reveal any evidence of publication bias.

### 4. Discussion

In this meta-analysis, nine studies comparing IV+ITH/IVT with IV monotherapy for post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria were systematically reviewed. MDR/XDR *A. baumannii* was the most commonly isolated bacterial agent. Polymyxins were the most common drug used for ITH/IVT, followed by aminoglycosides. The risk of mortality and microbiological clearance were significantly different between the two groups.

Post-neurosurgical intracranial infection has been classified as a nosocomial infection, and resistant Gram-negative bacteria and staphyloccoci are most likely to be the pathogenic agents [4]. MDR/XDR Gram-negative bacteria-related ventriculitis/meningitis has become increasingly frequent in recent years, among which *Acinetobacter* spp. are the most common organisms isolated in CSF cultures, followed by *K. pneumoniae* and *P. aeruginosa* [22,23]. Mortality due to *A. baumannii* ventriculitis/meningitis has been reported to be as high as 72.7\% [21]. A multicentre retrospective case-control study showed that even with IVT treatment, the mortality rate in patients with MDR/XDR *A. baumannii* central nervous system (CNS) infection reached 48\% [13].

Penetration of many drugs through the blood–brain barrier is poor, and the presence of MDR/XDR bacteria has forced the use of topical therapies to achieve an effective therapeutic concentration of antibiotics at the site of infection [11]. The most recent meta-analysis revealed an 84\% lower risk of mortality in the ITH/IVT+IV antimicrobial therapy group treated for post-neurosurgical *A. baumannii* infection [24]. ITH/IVT is usually used as a remedial treatment when systemic treatment is ineffective rather than as an initial treatment. A previous study showed that the mean time from diagnosis to initiation of ITH/IVT treatment was 25.4 days [25]. Compared with survival, death is associated with delayed ITH/IVT therapy [26], and early administration of effective ITH/IVT therapy might increase the clinical cure rate for post-neurosurgical intracranial infection [19,25]. However, there have been few clinical studies on the correlation between the timing of ITH/IVT administration and mortality to date.

The dosage regimen of ITH/IVT antimicrobial therapy is controversial because of the minimum inhibitory concentration (MIC) of the causative micro-organism, variable volumes of CSF, circulation and drainage of CSF, and differing degrees of meningeal inflammation [9,10]. Guidelines suggest that the IVT dosage of colistin or polymyxin B should be 10 mg or 5 mg daily and the duration of therapy should be 21 days for ventriculitis/meningitis caused by Gram-negative bacteria [4]. The dosages and treatment courses of polymyxins in studies included in the current review varied, indicating that the ITH/IVT administration of the drug was still based on expert opinion or clinical experience. The duration of therapy described was also quite variable (2–4 weeks). Shorter treatments
(<1 week) correlate with higher mortality, although death may occur for other potential reasons before the conclusion of the scheduled treatment in critically ill patients [27].

CSF sterilisation is likely to be an important factor for mortality [11]. A lack of CSF sterilisation with treatment may lead to increased mortality during hospitalisation [13]. In addition, seizures, subdural effusions and hemiparesis are found significantly more often in those with delayed CSF sterilisation [28]. ITH/IVT antibiotics can likely lead to rapid CSF sterilisation in post-neurosurgical patients with meningitis and ventriculitis. Remes et al. showed that the mean time necessary to obtain CSF sterilisation was 2.9 ± 2.7 days (range 1–12 days) of ITH/IVT administration of antibiotics in critically ill patients [29]. However, in other studies the mean time to CSF sterilisation was 4–21 days [8,14].

Adverse effects of ITH/IVT polymyxins are not negligible. Previous studies reported that toxicity was mostly caused by chemical meningitis (~15–60% of patients) and the occurrence of neurotoxicity was apparently dose-independent [7,30]. Most studies have shown that adverse effects are not observed or are mild [11,12,14,29]. Adverse effects following high-dose ITH/IVT antibiotics can lead to poor treatment outcomes owing to complications in critically ill patients [31]. In some critically ill patients who were mechanically ventilated and sedated, the signs or symptoms of CNS toxicity were ignored [9]. This indicates that ITH/IVT therapy is safe, but further well-designed studies are required to validate this.

This study has several limitations that need to be acknowledged. First, all of the studies included in the review were retrospective observational studies with small sample sizes. The possibility of unmeasured confounding factors between the two groups remains, although prospective RCTs for such studies are ethically difficult. Second, the total mortality data of the included studies was extracted. Some of the deaths were not directly related to intracranial infection but to the disease itself or to nosocomial pneumonia; however, these deaths do not affect the credibility of the results. Finally, we did not assess the association of antimicrobial choice and duration of treatment with outcome measures because it was difficult to define the optimal dosage, duration and indications in ITH/IVT antimicrobial therapy for post-neurosurgical intracranial infections in different studies.

Based on this meta-analysis, we conclude that ITH/IVT antimicrobial therapy is associated with a lower risk of mortality and a higher microbial clearance rate in patients with post-neurosurgical intracranial infections due to MDR/XDR Gram-negative bacteria. More prospective RCTs on this topic are urgently required to provide more conclusive guidelines for clinical practice.

Declaration

Funding: This study was supported by research grants from the Zhejiang Provincial Natural Science Foundation of China [LY15H310006 and LY16H310001] and the Department of Education of the Zhejiang Province of China [Y201328670].

Competing interests: None declared.

Ethical approval: Not required.

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