ORIGINAL ARTICLE

Intrathecal or intraventricular therapy for post-neurosurgical Gram-negative meningitis: matched cohort study

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Abstract

Gram-negative post-operative meningitis due to carbapenem-resistant bacteria (CR-GNPOM) is a dire complication of neurosurgical procedures. We performed a nested propensity-matched historical cohort study aimed at examining the possible benefit of intrathecal or intraventricular (IT/IV) antibiotic treatment for CR-GNPOM. We included consecutive adults with GNPOM in two centres between 2005 and 2014. Patients receiving combined systemic and IT/IV treatment were matched to patients receiving systemic treatment only. Matching was done based on the propensity of the patients to receive IT/IV treatment. We compared patient groups with 30-day mortality defined as the primary outcome. The cohort included 95 patients with GNPOM. Of them, 37 received IT/IV therapy in addition to systemic treatment (22 with colistin and 15 with amikacin), mostly as initial therapy, through indwelling cerebrospinal fluid drains. Variables associated with IT/IV therapy in the propensity score included no previous neurosurgery, time from admission to meningitis, presence of a urinary catheter and GNPOM caused by carbapenem-resistant Gram-negative bacteria. Following propensity matching, 23 patients given IT/IV therapy and 27 controls were analysed. Mortality was significantly lower with IT/IV therapy: 2/23 (8.7%) versus 9/27 (33.3%), propensity-adjusted OR 0.19, 95% CI 0.04–0.99. Death or neurological deterioration at 30 days, 14-day and in-hospital mortality were lower with IT/IV therapy (OR <0.4 for all) without statistically significant differences. Among patients discharged alive, those receiving IT/IV therapy did not experience more neurological deterioration. Serious adverse events with IT/IV therapy were not documented. Our results support the early use of IT antibiotic treatment for CR-GNPOM when a delivery method is available.

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Introduction

Central nervous system infections in patients undergoing neurosurgical procedures are a major cause of morbidity and mortality. In recent studies the reported rate of complications including meningitis, cerebral abscess, subdural empyema, bone-flap and wound infections was 0.8–4% [1–3]. Post-operative meningitis represents ~30% of all post-neurosurgical infections [4]. Carbapenem-resistant Gram-negative post-operative meningitis (CR-GNPOM) is associated with mortality rates of 60–70% [5].

Penetration of antibiotics into the cerebrospinal fluid (CSF) is poor, even during meningitis. This is especially problematic when GNPOM is caused by carbapenem-resistant Gram-negative bacteria (CRGN), as the penetration of aminoglycosides and colistin into the CSF is very poor. Colistin penetration

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into the CSF was estimated as 6–7% and 10–11% with and without meningitis, respectively [6,7]. Recent reviews recommend intrathecal or intraventricular (IT/IV) therapy for GNPOM, especially when a delivery method is already in place [8–10]. This statement, however, is based on case reports or small, and non-comparative case series. The possible detriments of IT/IV therapy include secondary infections and toxicity ranging from aseptic meningitis (in up to 25% of cases) to seizures (very rare) [10,11]. We investigated the utility of IT/IV therapy for CR-GNPOM in a retrospective cohort study.

Methods

Nested propensity-matched historical cohort study conducted in two primary and tertiary care hospitals serving as neurosurgical referral centres, Rambam Health Care Campus and Rabin Medical Centre, between the years 2005 and 2014. We included all consecutive adults with Gram-negative post-neurosurgical meningitis, using the CDC definitions for clinical bacterial meningitis [12]. Inclusion mandated isolation of Gram-negative bacteria from the CSF with or without positive blood cultures AND at least one of the following signs or symptoms: fever (>38°C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability AND at least one of the following: increased white blood cells, elevated protein, and/or decreased glucose in CSF, organisms seen on Gram stain of CSF, organisms cultured from blood AND a decision to treat made by the attending physician AND a neurosurgical procedure performed within the previous 30 days or within 1 year in the presence of a foreign body. We included patients more than once for different episodes of meningitis, where separate episodes were defined if more than 2 weeks have elapsed from the date of the last growth in the CSF for the first episode, and different bacteria were isolated on the second episode. Patients were identified through reports of the microbiology laboratory.

The exposure variable was IT/IV therapy in addition to systemic antibiotic therapy given at any time during the course of treatment. Systemic antibiotic therapy was given according to local guidelines. Empirical therapy consisted of ceftazidime and vancomycin twice daily or tailored to Gram stain results. Definitive therapy was directed by susceptibilities, with preference to the lowest spectrum β-lactam. Colistin was a last resort antibiotic for CRGNs and was administered alone. Antibiotics were dosed according to recommendations for meningitis. We matched patients who received IT/IV therapy to patients who received systemic therapy only by their propensity to receive IT/IV therapy. Outcomes were compared between patient groups in the nested propensity-matched cohort. The primary outcome assessed was 30-day mortality. Secondary outcomes included a composite of in-hospital death or neurological deterioration for patients discharged alive, 14-day mortality, in-hospital death, and neurological deterioration at discharge. Neurological deterioration was recorded on a four-grade scale (AVPU—Alert, Verbal, Pain, Unresponsive), with deterioration defined as at least 1 point decrease in the AVPU score from neurological status just before meningitis.

Univariate OR and 95% CI were calculated using binary logistic regression. The propensity score was computed using logistic regression including variables significantly associated with IT/IV therapy on univariate analysis and not clinically or statistically correlated. Its predictive performance was assessed using the area under the receiver-operating curve. Propensity matching was performed using the closest propensity score that did not differ by more than 0.01. If more than one control per case had identical propensity scores, all matching controls were included. The study was approved by the hospitals' institutional ethics committees waiving the need for informed consent given the non-interventional and retrospective design of the study.

Results

A total of 132 episodes of GNPOM in 117 patients were identified in both centres during the study period. Complete data regarding antibiotic treatment were available for 101 episodes (95 patients). Of them, 37 (36.6%) received IT/IV therapy in addition to systemic treatment, 22 with colistin (median dose 50 000 IU/day, range 50 000–250 000) and 15 with amikacin (median dose 37.5 mg/day, range 25–50 mg/day) for a total median duration of 9 and 12 days, respectively. In 31 (83%) patients IT/IV therapy was started initially or when culture results became available, whereas in 6 (17%) it was initiated following failure of systemic therapy. The IT/IV therapy was administered through pre-existing CSF drains and no drains were inserted especially for IT/IV therapy. In the overall cohort, 30-day mortality was 5/37 (13.5%) among patients treated with IT/IV therapy versus 15/64 (23.4%) among patients treated with systemic antibiotics alone.

Patients given IT/IV therapy had several adverse prognostic features compared with those treated with systemic antibiotics alone (Table 1). These included the time from admission to meningitis; presence of a urinary catheter before onset of meningitis; meningitis caused by *Acinetobacter baumannii* or by a CRGN; and higher protein levels, total leucocyte and neutrophil counts in the CSF. Patients receiving IT/IV therapy had poorer neurological status at meningitis onset, although this was not statistically significant. In addition, no previous hospitalization, independent living, and no previous neurosurgery, which were highly correlated, were more common in the IT/IV