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Short Communication

Clinical features and mortality of patients on renal replacement therapy receiving polymyxin B

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ABSTRACT

There are no clinical data for polymyxin B (PMB) in patients on renal replacement therapy (RRT). The aim of this study was to evaluate the characteristics of patients on RRT receiving PMB and to identify predictors of 30-day mortality, with special focus on dosage. A multicentre prospective cohort study including patients aged ≥18 years treated with PMB for ≥48 h while on any type of RRT was performed. In total, 88 patients were evaluated, including 34 (38.6%) on continuous venovenous haemodialysis (CVVH) and 54 (61.4%) on intermittent haemodialysis. Most patients (81.8%) received recommended doses between 1.5 mg/kg/day and 3.0 mg/kg/day. The 30-day mortality was 51.1% (45/88 patients). There was no significant association of dose (in mg/kg) with mortality. A PMB average daily dose ≥200 mg was predictive of decreased 30-day mortality in the multivariate model (hazard ratio = 0.35, 95% confidence interval 0.14–0.90; $P = 0.03$), whilst CVVH ($P = 0.04$), higher Charlson co-morbidity index ($P = 0.02$) and Acute Physiology and Chronic Health Evaluation (APACHE) II score ($P = 0.04$), and *Pseudomonas aeruginosa* infection ($P = 0.001$) were independent risk factors for mortality. The results were not changed by the inclusion of patient weight or dose (in mg/kg) in the model, although the latter was significantly correlated with total daily dose. This is the first clinical study to show that higher doses of PMB are associated with lower mortality in patients on RRT.

1. Introduction

Polymyxins, both polymyxin B (PMB) and polymyxin E (colistin), have been largely prescribed for infections by extensively drug-resistant Gram-negative bacteria worldwide [1–3]. However, colistin is still the most commonly used and studied polymyxin, including in patients on renal replacement therapy (RRT) [1–3].

It has been demonstrated that total body clearance of PMB is not dependent on creatinine clearance; thus, dose adjustment is not required for patients with renal dysfunction [4]. Moreover, a previous study showed that only 5% and 12% of PMB was cleared by dialysis in two patients on continuous venovenous haemodialysis (CVVH) [5]. Thus, the dosage of PMB should not be lowered in patients on RRT, and possibly an additional dose may be required [3]. Despite this, there are no published reports of patients on RRT treated with 'unadjusted' doses of this last-resort antibiotic.

Since the efficacy of polymyxins is related to the ratio of the free area under the concentration–time curve (*f*AUC) to the minimum inhibitory concentration of the causative pathogen (MIC), it is important to achieve an adequate time-averaged exposure to polymyxins [3]. Actually, some studies with PMB found that higher total daily doses were, or tended to be, associated with better outcomes despite the increased risk of nephrotoxicity [6,7].

In this study, we aimed (i) to evaluate the characteristics of patients on RRT treated with PMB in institutions where dose adjustment is not recommended for renal dysfunction or for any kind of RRT and (ii) to assess potential predictors of 30-day mortality.

2. Patients and methods

2.1. Study design, setting and participants

This was a multicentre prospective cohort study performed at three tertiary-care teaching hospitals in Porto Alegre, Brazil. The

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study was approved by the ethical committees of each hospital. All patients aged ≥18 years who received intravenous PMB from 1 February 2013 to 31 January 2014 while on any type of RRT were included in the study. Only patients who were on RRT before PMB initiation were eligible for the study. Patients were excluded if they received PMB for a period <48 h, if they died within the first 48 h of PMB initiation or if they did not fulfil any US Centers for Disease Control and Prevention (CDC) criteria [8] of infection (evaluated by our research team). In patients who had more than one treatment with PMB, only the first course was analysed. Institutional protocols recommended doses of 1.5–3.0 mg/kg actual body weight/day in two divided administrations with no dose adjustment recommended either for decreased creatinine clearance or for RRT. Loading doses were not administered. Doses were at the discretion of the attendant physician.

2.2. Variables and definitions

The outcome was 30-day mortality. The characteristics of the patients were evaluated addressing the following variables, which were all also considered potentially associated with 30-day mortality: demographics; actual body weight; severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [9] and co-morbidities as assessed by the Charlson co-morbidity index [10]; type of RRT; presence of septic shock at the beginning of therapy [11]; intensive care unit (ICU) admission at the time of PMB initiation; presence of mechanical ventilation at the beginning of PMB therapy; site of infection as defined by CDC criteria [8]; aetiology of the infection (specific organisms grown from a culture of the site of infection, and unknown when cultures yielded negative results or were not required by attendant physicians); presence of bacteraemia; combination therapy (second antimicrobial with anti-Gram-negative activity regardless of in vitro susceptibility administered concomitantly with PMB for ≥48 h); polymicrobial infections (infections by more than one organism recovered from the same site of infection, excluding coagulase-negative staphylococci in a single blood culture); concomitant infections at other sites by other micro-organisms; length of hospital stay prior to PMB initiation; reason for hospital admission (clinical versus surgical); reason for dialysis (chronic versus acute renal failure); and PMB doses. Dosages were evaluated as average daily dose of PMB (sum of total daily dose each day divided by the number of days until the end of therapy or death) and daily dose by mg/kg/day.

2.3. Microbiology

Isolates were identified by the VITEK® system (bioMérieux, Marcy-l'Étoile, France). Isolate susceptibility was tested by the disk diffusion method and was interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria [12], with the exception of PMB for *Acinetobacter baumannii* and Enterobacteriaceae isolates in which susceptibility to PMB was assessed by broth microdilution or Etest (bioMérieux) and an MIC ≤2 mg/L was considered susceptible.

2.4. Statistical analysis

All statistical analyses were carried out using PASW Statistics for Windows v.18.0 (SPSS Inc., Chicago, IL). Bivariate analysis was performed separately for each of the variables. *P*-values were calculated using χ^2 test or Fisher's exact test for categorical variables and using Student's *t*-test or Wilcoxon rank-sum test for continuous variables. Covariates were compared between 30-day survivors and non-survivors, and those with a *P*-value of ≤0.2 were included in a Cox proportional hazards model in a forward stepwise regression. Variables were checked for confounding and collinearity. Variables with a *P*-value of ≤0.10 were maintained in the model.

Subgroup analysis was performed for microbiologically confirmed infections, for patients admitted to the ICU and according to the type of dialysis.

Proportional hazards assumption was graphically checked inspecting the log[−log(S)] plot. Tests for interactions were not performed. All tests were two-tailed, and a *P*-value of ≤0.05 was considered statistically significant.

3. Results

A total of 96 patients received PMB for ≥48 h while on RRT during the study period. Of these, 8 were excluded because of a lack of defined CDC criteria for infection, resulting in 88 patients included in the analysis, including 34 patients (38.6%) on CVVH and 54 patients (61.4%) on intermittent haemodialysis. The 30-day mortality rate was 51.1% (45/88). Mortality rates according to total daily doses and doses in mg/kg are shown in Fig. 1. The characteristics of the 88 patients and their distribution according to 30-day mortality are given in Table 1. An average daily dose ≥200 mg was the only dose 'cut-off' that was associated with decreased 30-day mortality. The 14-day mortality was 42.0%: 35.3% (6/17) and 43.7% (31/71) in patients receiving doses ≥200 mg/day and <200 mg/day, respectively (*P* = 0.59).

In the multivariate analysis, a total daily dose ≥200 mg was the only variable associated with a decreased risk of 30-day mortality (Table 2). CVVH, higher Charlson co-morbidity index and APACHE II score, and *P. aeruginosa* infection increased such risk (Table 2). Inclusion of patient weight or dose in mg/kg into the model did not change the results (Table 2).

In patients receiving CVVH, the 30-day mortality rate was 64.7% (22/34): 22.7% and 77.3% in patients receiving PMB doses ≥200 mg and <200 mg, respectively (*P* = 0.45). In the group of patients on intermittent haemodialysis, the 30-day mortality rate was 42.6% (23/54): 0% and 48.9% in the ≥200 mg and <200 mg groups, respectively (*P* = 0.016).

Among the 52 patients with microbiologically confirmed infections, the median time to begin PMB therapy from the onset of infection was 3 days (interquartile range 1–4 days). Higher dose was not a statistically significant protective factor in this subgroup [hazard ratio (HR) = 0.39, 95% confidence interval (CI) 0.13–1.30; *P* = 0.12]. Among the 64 patients admitted to the ICU, PMB dose ≥200 mg was independently predictive of decreased 30-day mortality (HR = 0.33, 95% CI 0.11–0.97; *P* = 0.043).

4. Discussion

This study assessed the use of PMB in patients on RRT and found that patient co-morbidities, severity of illness, CVVH and *P. aeruginosa* infection significantly increased 30-day mortality. On the other hand, the study showed that a PMB dose ≥200 mg/day was independently associated with lower 30-day mortality, regardless of the type of dialysis. To our knowledge, this is the first clinical study to show that higher doses of PMB (mostly unadjusted; only seven patients received doses <1.5 mg/kg/day) were associated with lower mortality in patients on RRT.

A PMB dose ≥200 mg/day has previously been found to be significantly associated with lower in-hospital mortality rates [6], supporting, as in the current study, the pre-clinical finding that *f*AUC/MIC is the pharmacokinetic/pharmacodynamic index that best correlates with polymyxin activity [13,14]. It is interesting that although total body weight was shown to be related to PMB total body clearance [5], a daily dose ≥200 mg remained an independent protective factor regardless of patient body weight.