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Short report

Efficacy of antibiotic prophylaxis against ventilator-associated pneumonia

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SUMMARY

Ventilator-associated pneumonia (VAP) is one of the most important problems of intensive care units. Eighty-four neurologic patients with acute stroke (Glasgow Coma Score ≤8) were entered into a double-blind clinical trial. Patients in the intervention group received piperacillin–tazobactam 4 g/0.5 g at the time of intubation and 12 h later. The incidences of early-onset (within four days of intubation) and late-onset VAP were 9.2 and 26.9 episodes per 1000 days of mechanical ventilation in the intervention and control groups, respectively (odds ratio: 0.217; 95% confidence interval: 0.056–0.085; $P = 0.028$). Administration of prophylactic piperacillin–tazobactam may reduce early-onset VAP, but the benefit does not extend to late-onset VAP.

Introduction

Healthcare-acquired infections (HCAIs) remain an important problem globally, and are a particular risk for patients in intensive care units (ICUs). Whereas ICUs account for only around 5–15% of hospital beds, more than 30% of HCAIs are ICU-related. Ventilator-associated pneumonia (VAP) is the most frequent and important ICU-acquired infection. It may occur relatively early after intubation, has an incidence of 9–27% in mechanically ventilated patients, and has a mortality rate of 30–70%. Reasons for these wide differences include differences in the type of ICU and the diagnostic criteria used in studies. Since the upper respiratory tract is the source of the bacteria that cause VAP, preventive strategies have been used to reduce the microbial load here. These strategies include oral decontamination and selective bowel decontamination. However, these strategies have limited efficacy, especially in the prevention of early-onset (EO)-VAP [1–5].

The aim of this study was to determine the effectiveness of antibiotic prophylaxis with piperacillin–tazobactam in preventing EO-VAP in ventilated patients with stroke.

Methods

This double-blinded clinical trial was conducted between April 2014 and September 2015 in stroke patients ventilated on

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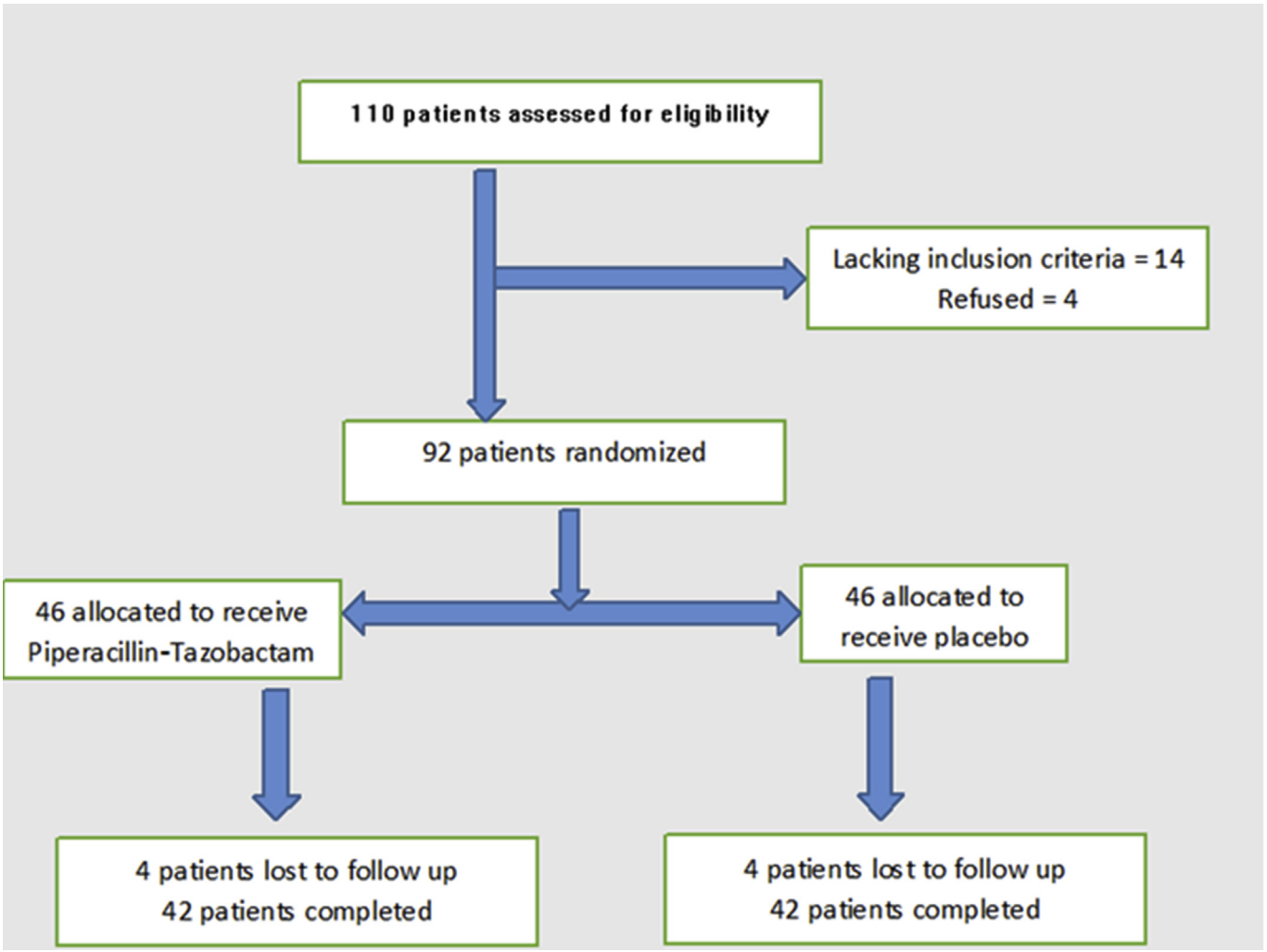

Figure 1. Flow chart of patients participating in the study.

the adult medical ICU of a university hospital in Iran. Written informed consent was obtained in all cases from the patient's legal guardian.

The study was approved by the Ethics committee of Arak University of Medical Sciences and was registered in the clinical trial registry with registration number ID: IRCT201407029855N6.

Patients aged >20 years with Glasgow Coma Scale (GCS) ≤8, and with hospital stay <48 h, were eligible for inclusion in the study. Exclusion criteria were sensitivity to piperacillin–tazobactam, end-stage renal disease, immune deficiency, intubation for reasons other than stroke, hospitalization more than 48 h before intubation, receiving antibiotics prior to intubation, commencement of antibiotics for any other reason, and candidates for organ donation.

According to data from one previous study that reported a reduction in EO-VAP from 22.4% in the control group to 2.8% in the intervention group, and considering the α-level of 0.05 and power of 80%, the sample size was calculated as follows [4]:

$$N_1 = N_2 = (Z_{\alpha/2} + Z_{\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2)]/(p_1 - p_2)^2 = 42.$$

Allowing for a 10% drop-out rate, 92 patients were enrolled. Patients were randomly assigned to receive either the piperacillin–tazobactam or placebo (normal saline). The computer-generated randomization was 1:1 for the two groups (Figure 1). Patients in the intervention group received 4.5 g piperacillin–tazobactam at the time of intubation and 12 h later; patients in the control group received equal volumes of normal saline at the same times.

Ventilator-associated pneumonia refers to pneumonia that arises more than 48 h after endotracheal intubation. VAP was presumed if new or progressive consolidation or infiltrates appeared on chest radiographs in the presence of two of the following: fever ≥38°C or hypothermia <36°C, leucocytes ≥11,000/mm^3 or ≤4000/mm^3, or new onset of purulent endotracheal secretions or change in the character of sputum. Pneumonia was considered definite in the presence of either a quantitative culture of tracheal aspirate ≥10^6 colony-forming units (cfu)/mL or a quantitative culture of a protected specimen brush ≥10^3 cfu/mL or a quantitative bronchoalveolar lavage culture ≥10^4 cfu/mL. VAP was defined as early-onset when it developed in the first four days of hospitalization and as late-onset when it appeared after the fourth day [5].

Demographic data including age, gender, and any underlying medical conditions were recorded. On the first day, a chest X-ray was performed for all patients. Complete blood count, erythrocyte sedimentation rate, and C-reactive protein were measured at baseline, and were routinely rechecked at days 2, 3, and 7. In cases of fever or leucocytosis, urine culture, blood cultures, and chest X-ray were performed. In cases where there was an increase in respiratory secretions or an abnormal chest X-ray, VAP was suspected, and airway secretions were obtained through tracheal aspiration or bronchoalveolar lavage and sent for quantitative culture. The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated during the first days of admission. The SOFA score has a range of 0–4 points for each of the six organ systems (neurologic, cardiovascular, respiratory coagulation, renal, and hepatic). The APACHE II score is composed of 12 physiological variables and two disease-related variables were recorded on admission [6].

The rate of early and late-onset VAP, the ICU length of stay, and the mortality rate were evaluated in both groups. Statistical analyses were performed using the statistical software package SPSS, version 18 (SPSS Inc., Chicago, IL, USA). The data were summarized and differences between the groups were compared by Fisher's exact test or χ^2-test for categorical variables and *t*-test or Mann–Whitney test for continuous variables depending on the results of the Kolmogorov–Smirnov test for normality of distributions. Differences in length of stay between two groups were compared by a log-rank test and repeated-measures analysis of variance was used to test for difference between group means over time. We used Kaplan–Meier curves and the log-rank test to compare the number of pneumonia-free days in the first two weeks between the two groups. A propensity-score regression analysis was applied to assess the effect of piperacillin–tazobactam prophylaxis on early-onset VAP development. For all analyses, $P < 0.05$ was considered significant.

Results

Ninety-two patients, comatose due to a cerebrovascular accident in the ICU, entered the study, among which eight patients were later excluded. Baseline characteristics and microbiology data are shown in Table I. The incidence of early VAP was 9.2 episodes per 1000 days of mechanical ventilation in the intervention group and 26.9 episodes per 1000 days of mechanical ventilation in the control group (odds ratio (OR): 0.22; 95% confidence interval (CI): 0.06–0.09; $P = 0.028$). The incidence of late VAP was 21.7 episodes per 1000 days of mechanical ventilation in the intervention group and 19.6 episodes per 1000 days of mechanical ventilation in the control group (OR: 0.85; 95% CI: 0.28–2.60; $P = 0.776$). The overall VAP incidence was 30.9 episodes per 1000 days of mechanical ventilation in the intervention group and 46.6 episodes per 1000 days of mechanical ventilation in the control group (OR: 0.38; 95% CI: 0.15–0.96; $P = 0.041$).

The mean length of hospital stay was 32.9 ± 21.9 days in the intervention group and 45.8 ± 28.1 days in the control group ($P = 0.026$). The mean length of ICU stay was 20.4 ± 17.3 days in intervention and 29.2 ± 21.3 days in the control group ($P = 0.041$). The mean duration of mechanical ventilation was 18.7 ± 12.5 days in the intervention group and 26.1 ± 21.9 days in the control group ($P = 0.088$). The number of pneumonia-free days during the first week was higher in the intervention group (log-rank test: $P = 0.034$). The propensity-score regression analysis by balancing observed covariates between subjects in control and intervention study groups showed that piperacillin–tazobactam prophylaxis was independently associated with a lower incidence of EO-VAP (OR: 0.27; 95% CI: 0.09–0.84; $P = 0.024$).

Table I
Baseline characteristics of patients studied

Characteristics	Intervention group	Control group	*P*-value
Age (years)[a]	65.6 ± 23.9	67.2 ± 21	0.739
Sex			
Male	29 (69%)	22 (52.4%)	0.118
Female	13 (31%)	20 (47.6%)	
Initial GCS[a]	6 ± 1.3	6.2 ± 1.5	0.517
APACHE II[a]	18.2 ± 6.7	17.7 ± 7.2	0.743
SOFA score[a]	11.2 ± 3.5	10.7 ± 3.2	0.496
Neurosurgical intervention	9 (21.4%)	10 (23.8%)	0.794
Underlying diseases			
Hypertension	15 (35.7%)	16 (38.1%)	0.818
Diabetes mellitus	13 (30.9%)	16 (38.1%)	0.49
Coronary artery disease	11 (26.2%)	13 (30.9%)	0.631
Respiratory disease	11 (26.2%)	8 (19.0%)	0.435
Smoker	20 (47.6%)	18 (42.8%)	0.661

GCS Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.
[a] Mean ± SD.

In the three patients with EO-VAP in the intervention group, *Staphylococcus aureus* (two patients) and *Streptococcus pneumoniae* (one patient) were isolated. Among the 11 patients in the control group with EO-VAP the causative microorganisms isolated were *S. pneumoniae* (three patients), *S. aureus* (three patients), *Klebsiella pneumoniae* (two patients), *Pseudomonas aeruginosa* plus *Escherichia coli* (one patient), and *Acinetobacter baumannii* (two patients). Gram-negative bacteria predominated in LO-VAP in both groups, including *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *Serratia marcescens*.

In the first week of ICU care, four patients (9.5%) in the intervention group and nine patients (21.4%) in the control group died (OR: 1.91; 95% CI: 0.53–6.87; $P = 0.131$). Overall hospital mortality was 40.5% (17 patients) in the intervention group and 52.4% (22 patients) in the control group (OR: 0.62; 95% CI: 0.26–1.47; $P = 0.274$). The main causes of death were sepsis and septic shock (30.8%), cerebral anoxia (26.9%), brain death (15.4%), acute respiratory distress syndrome (15.4%), and cerebral haemorrhage (11.5%).

Discussion

Ventilator-associated pneumonia is a frequent problem in ICU patients that has been associated with increased length of hospital stay, healthcare costs, and mortality [6,7]. Various preventive measures have been used to address this problem, but few studies have evaluated intravenous prophylactic antibiotics. We investigated the use of prophylactic piperacillin–tazobactam in a group of patients who seemed to be at particularly high risk of developing VAP, finding that although

the incidence of EO-VAP and lengths of stay in ICU and hospital were significantly lower in the intervention group, there were no significant differences in rates of LO-VAP, duration of mechanical ventilation, or of mortality. The latter observation could be because most deaths were due to non-infectious causes, and our study was not powered to detect differences in infection-related mortality.

In the study of Valles *et al*. in which the patients received an intravenous prophylactic antibiotic within the first 4 h after tracheal intubation, the incidence of EO-VAP in the intervention group was significantly lower than in control subjects [8]. As in our study, no significant difference in the incidence of late-onset VAP and mortality was observed. Sirvent *et al*. administered intravenous cefuroxime 1.5 g just 12 h after intubation [9]. Again, the incidence of EO-VAP was significantly lower in the treatment group. In another study, Acquarello *et al*. investigated three-day prophylaxis with ampicillin/sulbactam in coma patients and showed, as in our study, that the incidence of EO-VAP in the intervention group was significantly lower [10]. Whether antibiotic prophylaxis induces bacterial resistance is a well-founded concern. However, the use of one- or two-dose prophylactic antibiotic regimens may not be as deleterious to the patient as more prolonged treatment for patients who develop VAP. However, it seems that the impact of prophylaxis does not last long beyond cessation of treatment, in that we found no difference in rates of LO-VAP between the two groups. Antibiotic-related side-effects are another risk of administration of prophylactic antibiotics, but our admittedly small study detected no adverse effects. Further larger studies are required to determine whether the reductions in lengths of stay that were observed in the prophylaxis arm were an effect of the intervention.

The main limitations of our study were the small size and the lack of use of bronchoalveolar lavage to obtain samples in every case of suspected infection. Nevertheless, our study suggests that there may be limited benefit in using antibiotics as prophylaxis against VAP in stroke patients who are likely to require ventilation for a relatively prolonged period.

In conclusion, this study found that piperacillin—tazobactam prophylaxis in comatose patients reduced the incidence of EO-VAP and decreased the lengths of stay in ICU and hospital, but did not prevent LO-VAP. Larger randomized trials would be needed to confirm these findings, and to evaluate further the risks and benefits of using antibiotic prophylaxis in this setting.

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Conflict of interest statement
None declared.

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