American Journal of Emergency Medicine 35 (2017) 245–248

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Linezolid versus vancomycin for nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* in the elderly: A retrospective cohort analysis
Effectiveness of linezolid in the elderly

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ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form 21 October 2016
Accepted 27 October 2016

Keywords:
Methicillin-resistant *Staphylococcus aureus*
Nosocomial pneumonia
Linezolid
Vancomycin
Sequential organ failure assessment

ABSTRACT

Objectives: Several reports have compared the efficacy of linezolid (LZD) in Methicillin-resistant *Staphylococcus aureus* (MRSA) infections with that of vancomycin (VCM); however, these two antibiotics for the treatment of nosocomial MRSA pneumonia in elderly patients has not been well evaluated. The purpose of this study is to evaluate the efficacy and safety of LZD compared with VCM for the treatment of elderly patients with nosocomial MRSA pneumonia in a retrospective chart review of a cohort.
Methods: We included 28 consecutive patients aged ≥65 years hospitalized with a confirmed diagnosis of MRSA pneumonia and treated with LZD ($n = 11$) or VCM ($n = 17$) between November 2010 and May 2015. We collected patient, disease, and laboratory data. The primary outcome was 30-day mortality. The secondary outcomes were the sequential organ failure assessment (SOFA) total, respiratory, renal, coagulation, hepatic, cardiovascular, and central nervous system scores on days 1, 3, 7, and 14.
Results: There were no significant differences between the two groups with regard to baseline characteristics. The 30-day mortality rate was significantly lower in the LZD group than in the VCM group (0% vs. 41%, $P = .02$). The SOFA total score on days 3, 7, and 14 were significantly lower those at baseline in the LZD group ($P < .05$). The SOFA respiratory score on days 14 was also significantly lower than baseline in the LZD group ($P < .05$).
Conclusion: LZD may be more efficacious than VCM for treating elderly patients with nosocomial MRSA pneumonia.

1. Introduction

Among hospital-acquired infections, nosocomial pneumonia is the leading cause of death, with estimates of mortality ranging from 20% to 50% [1-4]. The clinical characteristics of pneumonia differ substantially between elderly and younger patients [5], and with the rapid aging of society, increasing numbers of elderly patients are experiencing nosocomial pneumonia. However, details of nosocomial pneumonia in the elderly remain unknown and need to be investigated.

Methicillin-resistant *Staphylococcus aureus* (MRSA) now accounts for 20%–40% of all nosocomial pneumonias [6,7]. The Clinical Practice Guidelines of the Infectious Diseases Society of America [8] recommend linezolid (LZD) and vancomycin (VCM) as first-line therapy for nosocomial MRSA pneumonia. Several reports have compared the efficacy of LZD in MRSA infections with that of VCM [9-19]. Wunderink et al. combined and analyzed the results of two RCTs comparing LZD with VCM in patients with nosocomial MRSA pneumonia (approximately 70% of whom were older than 65 years) [11,13] and concluded that initial therapy with LZD was associated with significantly better survival and clinical cure rates than was VCM in these patients [16]; however, these two antibiotics for the treatment of nosocomial MRSA pneumonia limited to elderly patients has not been well evaluated.

The objective of the present study was to evaluate the efficacy and safety of LZD for the treatment of elderly patients with nosocomial MRSA pneumonia in a retrospective chart review of a cohort. VCM

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http://dx.doi.org/10.1016/j.ajem.2016.10.058
0735-6757/

was chosen as the comparator as it is the global standard therapeutic drug for MRSA pneumonia.

2. Materials and Methods

2.1. Study Design and Setting

This single-center retrospective cohort study, which was performed by the review of medical records, was conducted at the National Hospital Organization Disaster Medical Center, a 455-bed academic teaching institution and with 34 ICU beds. It was approved by the center's institutional review board and was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The requirement for patient consent was waived due to the retrospective nature of the study.

2.2. Study Participants and Inclusion Criteria

We included consecutive patients aged 65 years or more who were hospitalized with a confirmed diagnosis of MRSA pneumonia and treated with VCM or LZD between November 1, 2010 and May 31, 2015. Diagnosis of MRSA pneumonia was made with clinical signs and symptoms acquired after hospitalization period of >48 h. The criteria was as follows: the presence of new infiltrate on chest X-ray together with at least one major criterion (i.e., fever ≥ 38.0 °C, hypothermia < 35.0 °C, cough, or pleuritic pain) or two minor criteria (i.e., dyspnea, leukocytosis > 12,000 cells/mm^3, altered level of consciousness, auscultatory signs of consolidation, or expectoration), and identification of MRSA isolated from cultures of respiratory tract, sputum, and blood samples [11,20]. Patients were excluded if they were considered as colonization or treated with teicoplanin.

2.3. Management of MRSA Pneumonia

Both VCM and LZD were considered as first-line treatment for nosocomial MRSA pneumonia at the discretion of the attending physician [21]. For VCM, the dosage was adjusted according to therapeutic drug monitoring. Treatment was designed to obtain a trough level of VCM between 15 and 20 μg/ml. The dosage of VCM was 1–2 g per day. LZD was administered at 600 mg every 12 h.

2.4. Data Sampling

The following data were collected from the medical records: age, sex, body mass index (BMI); baseline diseases such as chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver failure, and diabetic mellitus and laboratory data such as serum C-reactive protein, total serum bilirubin, and serum albumin level. We also recorded intensive care unit (ICU) admission rate, 30-day mortality and collected sequential organ failure assessment (SOFA) total, respiratory, renal, coagulation, hepatic, cardiovascular, and central nervous system scores at baseline and at days 1, 3, 7 and 14 after commencing administration of the antibiotic (LZD or VCM).

2.5. Outcome Measures

The primary outcome was 30-day mortality. The secondary outcomes were the SOFA total, respiratory, renal, coagulation, hepatic, cardiovascular, and central nervous system scores at days 1, 3, 7 and 14 after commencing administration of the antibiotic. These outcomes were compared between the LZD and VCM groups.

2.6. Statistical Analysis

Data are expressed as group means ± standard error of the mean or percentages as appropriate. Continuous variables were compared between groups using Student's *t* test or the Mann–Whitney *U* test. Categorical variables were analyzed using Fisher's exact test. The SOFA total, respiratory, renal, coagulation, hepatic, cardiovascular, and central nervous system scores were analyzed by two-way repeated-measures analysis of variance (ANOVA) for antibiotic type and time after the start of administration. The SOFA scores were compared using the Wilcoxon signed-rank test. The multiple imputations method for missing data was used in the analysis. Missing samples occurred because of death, and discharge from hospital.

A P value < 05 was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [22].

3. Results

3.1. Baseline Characteristics

In total, 28 patients were included: 11 patients were treated with LZD (the LZD group) and 17 with VCM (the VCM group). The baseline characteristics of the two groups are shown in Table 1. There were no significant differences between the two groups with regard to age, sex, BMI, baseline diseases, laboratory data, baseline SOFA scores, or ICU admission rate.

3.2. Effect of Treatment on 30-Day Mortality

The 30-day mortality rates were 0% (0 of 11 patients) and 41% (7 of 17 patients) in the LZD and VCM groups, respectively ($P = .02$).

3.3. Effect of Treatment on SOFA Total Scores

The serial changes in SOFA total score in the two groups are shown in Fig. 1. In the LZD group, this score decreased rapidly and consistently from baseline, indicating a decreasing risk of mortality. Repeated-measures ANOVA showed a significant difference between the two groups ($P < .01$). There was no interaction between treatment and time ($P = .08$). There were significant differences in the scores between

Table 1
Baseline patient characteristics in the two groups.

Characteristics	VCM group ($n = 17$)	LZD group ($n = 11$)	P value
Age, years	76.8 ± 1.9	77.0 ± 2.2	1.00
Gender (male/female)	14/3	10/1	1.00
BMI (kg/m^2)	21.0 ± 1.5	23.4 ± 1.3	0.16
Baseline diseases			
Chronic heart failure, %	1 (6)	2 (18)	0.54
COPD, %	1 (6)	0 (0)	1.00
CKD, %	2 (12)	2 (18)	1.00
Chronic liver failure, %	0 (0)	1 (9)	0.39
Diabetes mellitus, %	2 (12)	4 (36)	0.17
Laboratory date			
CRP (mg/dl)	10.9 ± 1.9	13.1 ± 2.6	0.40
eGFR (ml/min/1.73 m^2)	92.8 ± 11.4	60.7 ± 13.5	0.11
T-Bil (mg/dl)	0.93 ± 0.7	2.7 ± 1.5	0.40
Plt (10^3/μl)	22.7 ± 3.1	21.5 ± 2.9	1.00
Alb (g/dl)	2.3 ± 0.1	2.3 ± 0.2	0.87
SOFA score	4.6 ± 0.7	5.3 ± 1.1	0.72
ICU admission	3 (18)	6 (55)	0.09
30-Day mortality, %	7 (41)	0 (0)	0.02

Alb, albumin; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LZD, linezolid; Plt, platelet count; SOFA, sequential organ failure assessment score; T-Bil, total-bilirubin; VCM, vancomycin.
Data are expressed as group mean ± standard error or number (%).