European Review for Medical and Pharmacological Sciences 2017; 21: 3974-3979

Linezolid *vs.* vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis

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Abstract. – OBJECTIVE: This study aims to explore the treatment of methicillin-resistant staphylococcus aureus (MRSA) infection by using meta-analysis method.

MATERIALS AND METHODS: Pubmed/Medline, ScienceDirect, CNKI and Wanfang database were comprehensively searched to obtain the randomized controlled trials (RCTs) on linezolid and vancomycin in the treatment of MRSA infections. We extracted features and information of included studies and selected appropriate effect models based on the heterogeneity test results. The funnel plot was used to analyze publication bias.

RESULTS: A total of seven RCTs including 5376 cases met the inclusion criteria. Meta-analysis showed that the clinical cure rate of linezolid group was higher than that of vancomycin group after treatment (OR = 1.85; 95% CI: 1.33-2.59, $p<0.001$) and follow-up (OR = 1.49; 95% CI: 1.17-1.91, $p=0.001$). In the microbiologically evaluable patients, end of therapy (EOT) MRSA clearance rate, and test of cure (TOC) MRSA clearance rate of linezolid were superior to those of vancomycin.

CONCLUSIONS: Based on the combined analysis of randomized controlled trials, the efficacy of linezolid should be better than that of vancomycin in the treatment of infections caused by MRSA, but conclusions still need to be further validated by more well-designed RCTs of a large sample.

Key Words:
Linezolid, Vancomycin, Meta-analysis, Methicillin-resistant staphylococcus aureus.

Introduction

Since methicillin-resistant staphylococcus aureus (MRSA) was firstly discovered in 1960, it has become a major pathogen of community and hospital infections on a global scale[1,2]. It can cause a variety of infections, including skin and soft tissue infections (SSTIs), pneumonia, endocarditis, bacteremia, and osteomyelitis. The multi-drug resistance and high-extent resistance of MRSA bring many difficulties to infection control. Therefore, health care costs have increased rapidly, and the mortality rate has also gradually increased. Moreover, the strain has a strong ability to adapt to the environment factors and easily spread in the hospital. Historically, vancomycin has always been the drug of choice used to treat MRSA infections[3]. However, since the first staphylococcus aureus (VISA) with low-sensitivity to vancomycin was discovered in 1996, more and more VISA and vancomycin-resistant staphylococcus aureus (VRSA) have been reported[4]. The status of vancomycin as gold standard to treat MRSA has been challenged. Therefore, some new antimicrobial agents are introduced into the treatment of MRSA infections, in which linezolid has obvious advantages[5-8]. It has excellent antibacterial activity *in vitro* and *in vivo*, and is less prone to the cross-resistance with other antimicrobial drugs of inhibiting protein synthesis. With the increasing use of linezolid, in the past ten years, a number of clinical trials have been conducted to compare the efficacy and safety of linezolid and vancomycin in the treatment of gram-positive bacterial infections (including MRSA infection)[9-17]. However, the results are not exactly the same, which not come to a strong conclusion. Therefore, we collected these rigorously designed randomized controlled trials to perform a meta-analysis to systematical-

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ly evaluate the efficacy and safety of linezolid and vancomycin in treating the infections caused by MRSA.

Materials and Methods

Literature Search Strategy

PubMed, Medline, ScienceDirect, CNKI and Wanfang database were retrieved systematically from database building to September 2015. The search terms include "linezolid and vancomycin", "MRSA", "pneumonia", "*bacteraemia*", "skin and soft tissue infections", and "clinic trial". The published language and publication year were unlimited.

Document Inclusion Criteria

(1) Data were complete, prospective randomized controlled trials, one control group at least; (2) interventions were comparable, exposure to the same environment, in terms of linezolid and vancomycin in the treatment of bacterial infections, pathogens at least contained MRSA; (3) the original documents have clear outcome variables (clinical cure rate, microbiological clearance rate, and the incidence of adverse reactions).

Document Exclusion Criteria

(1) Experimental trials; (2) subjects were cancer patients or patients with neutropenia; (3) paired trials of linezolid or vancomycin with other antibiotics; (4) the trials focused on pharmacokinetics or pharmacodynamics.

Quality Assessment

Quality of each RCT was assessed by two reviewers independently according to the quality evaluation criteria in Cochrane systematic review's Manual 5.0.2. Jadad score method was used to evaluate the methodological quality of the included studies, which was divided into 1-5 points (1-2: low quality study, 3-4: medium quality study, 5: high-quality study). The evaluation content included whether randomized assignment and blinding method were used, whether the concealment method was appropriate, whether the quitting or lost cases were described. If the score was less than 2 points, it was removed.

Outcomes

The outcome includes the following: (1) the clinical cure rate of clinical evaluable patients (subjects with clinical manifestations that met the inclusion criteria and exclusion criteria) after treatment and follow-up; (2) MRSA clearance rate after follow-up; (3) mortality after follow-up; (4) adverse reactions.

Data Extraction

After reading the full text, data extraction was performed by two reviewers independently according to uniform standards. The contents included clinical characteristics (cases, sex ratio, and average age), intervention characteristics (interventions, dose, and courses), and clinical results (cured cases, microbiological bacterial clearance cases, dead cases and cases of adverse reactions). Any disagreements about data extraction were resolved by discussion.

Statistical Analysis

RevMan 5.2 software (London, UK) was used for statistical analysis; relative risk (RR) was used as the analysis statistics; 95% confidence interval (CI) was used to assess the efficacy and safety. Heterogeneity between trials was evaluated using I2; I2=0 indicated that various studies were homogeneous; <25% indicated no heterogeneity, 25-50% indicated mild heterogeneity; 50-75% indicated moderate heterogeneity; >75% indicated relatively large heterogeneity; according to the Cochrane Handbook, I2<50% is generally considered no heterogeneity between studies. If there was no heterogeneity, a fixed effects model was choosen; if there was heterogeneity, subgroup analysis and sensitivity analysis were performed to detect possible causes of clinical heterogeneity and statistical heterogeneity; if the results still had heterogeneity after excluding the interference of these factors, a random effects model was used for combined analysis. Publication bias was intuitively reflected using the funnel plot: the distribution morphology of clinical data was analyzed to determine whether there is publication bias; if there was no publication bias, funnel plot was normal.

Results

Document Creening Results

According to the search strategy, 88 relevant RCTs were obtained. After excluding animal study, subjects <13 years old, paired trials with other antibiotics, a total of 32 documents were primarily screened. After cursory reading, 21 studies were excluded, including 7 duplicated studies, 7 studies

Table I. The characteristics of included studies.

Publications	Study type	Number	Population	Therapy		Quality scores of group
				Linezolid group	Vancomycin group	
Wilcox et al[13]	Multi-center, RCT	363/363	Suspected related-MRSA blood infection or complex skin infection	Intravenous drip: 600 mg q12h, 7-28d	Intravenous drip: 1g, q12h, 7-28 d	3
Wunderink et al[15]	Multi-center, RCT	74/72	Suspected related-MRSA pneumonia	Intravenous drip: 600 mg q12h, 7-14d	Intravenous drip: 1g, q12h, 7-14 d	4
Kohno et al[10]	Multi-center, RCT	100/51	Definite or suspected MRSA related pneumonia or infection in soft tissue	Intravenous drip or Oral: 600 mg q12h, 7-28d	Intravenous drip: 1g, q12h, 7-28 d	4
Weigeltet et al[12]	Multi-center, RCT	592/588	Suspected MRSA related infection in soft tissue	Intravenous drip: 600 mg, q12h, 7-14d	Intravenous drip: 1g, q12h, 7-14 d	4
Wunderink et al[14]	Multi-center, double-blind RCT	321/302	Hospital acquired pneumonia	Intravenous drip: 600 mg, q12h, 7-21d	Intravenous drip: 1g, q12h, 7-21 d	3
Weigeltet et al[16]	Multi-center, RCT	66/69	Suspected MRSA related infection	Intravenous drip or Oral: 600 mg q12h, 7-14 d	Intravenous drip: 1g, q12h, 7-14 d	4
Stevens et al[11]	Multi-center, RCT	240/220	Suspected related-MRSA pneumonia, Bacteremia	Intravenous drip: 600 mg, q12h; Oral: 600 mg q12h, 7-14 d	Intravenous drip: 1g,q12h, 7-14 d	3

on hospitalized time and cost-benefit analysis and 7 pharmacokinetic or pharmacodynamics studies. In the remaining 11 documents, 4 literatures were further excluded since they had no MRSA results, with sample size <10 and with cancer patients as subjects. Finally, a total of seven valid documents[9-15] meeting the inclusion criteria were included. A total of 7 RCTs included a total of 5376 patients. The characteristics of included studies were shown in Table I. The allocation concealment of 7 randomized controlled trials was inappropriate. Only two trials used double-blind control method and five trials specifically described the quitting and lost cases. Linezolid-treated patients received 600 mg of linezolid q12h orally or intravenously, and vancomycin treatment group received vancomycin 1 g or 15 mg/kg q12h intravenously. Antimicrobial therapy was performed for 7-28 d. There were no significant differences between the two groups in age.

Clinical Outcomes of Meta-Analysis

A total of four studies reported the clinical cure rate of end of therapy (EOT) in clinically evaluable (CE) patients. It was better in linezolid group than that in vancomycin group (RR=1.85; 95% CI; 1.33-2.59; p=0.0002) (Figure 1A). A total of 7 studies reported the clinical cure rate of test of cure (TOC) in CE patients after follow-up. The result suggested that linezolid group was superior to vancomycin group (RR = 1.49; 95% CI; 1.17-1.91, p<0.001) in cure rate (Figure 1B).

MRSA Clearance rate of Meta-Analysis

A total of 3 studies reported MRSA clearance rate. It was higher in linezolid group than in vancomycin group (RR = 5.23; 95% CI; 2.30-11.87; p<0.001, Figure 2A). A total of 7 studies reported MRSA clearance rate of microbe-evaluable TOC patients. The meta-analysis suggested that it was higher in linezolid group than in vancomycin group (RR = 1.55; 95% CI; 1.09-2.21; p=0.01, Figure 2B).

Publication bias analysis

As shown in Figure 3, the inverted funnel plot was symmetrical, suggesting the absence of publication bias.

Discussion

In this study, a systematic review of 7 randomized controlled trials was performed to compare the efficacy and safety of linezolid, and

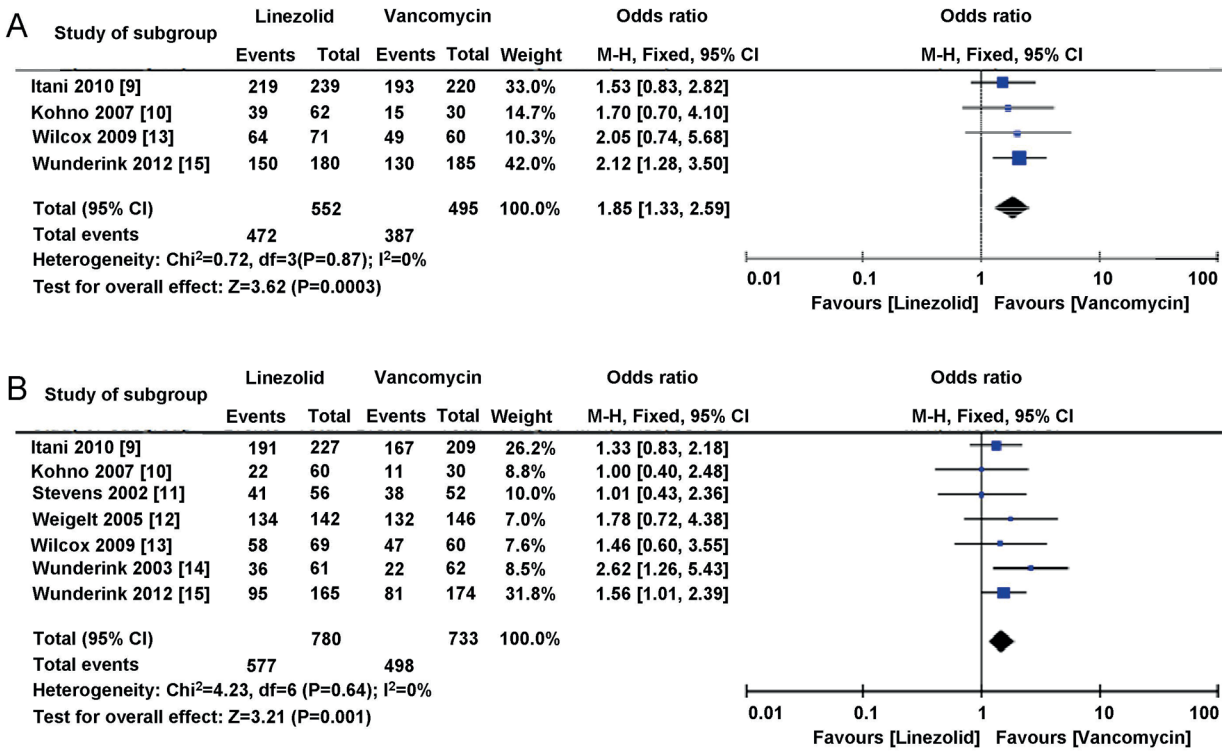

Figure 1. Forest plot of effect comparison between linezolid group and vancomycin group in clinical cure rate. ***A***, the clinical cure rate of EOT in CE patients; ***B***, clinical cure rate of TOC in CE patients after follow-up. EOT: end of therapy, TOC: test of cure, CE: clinically evaluable.

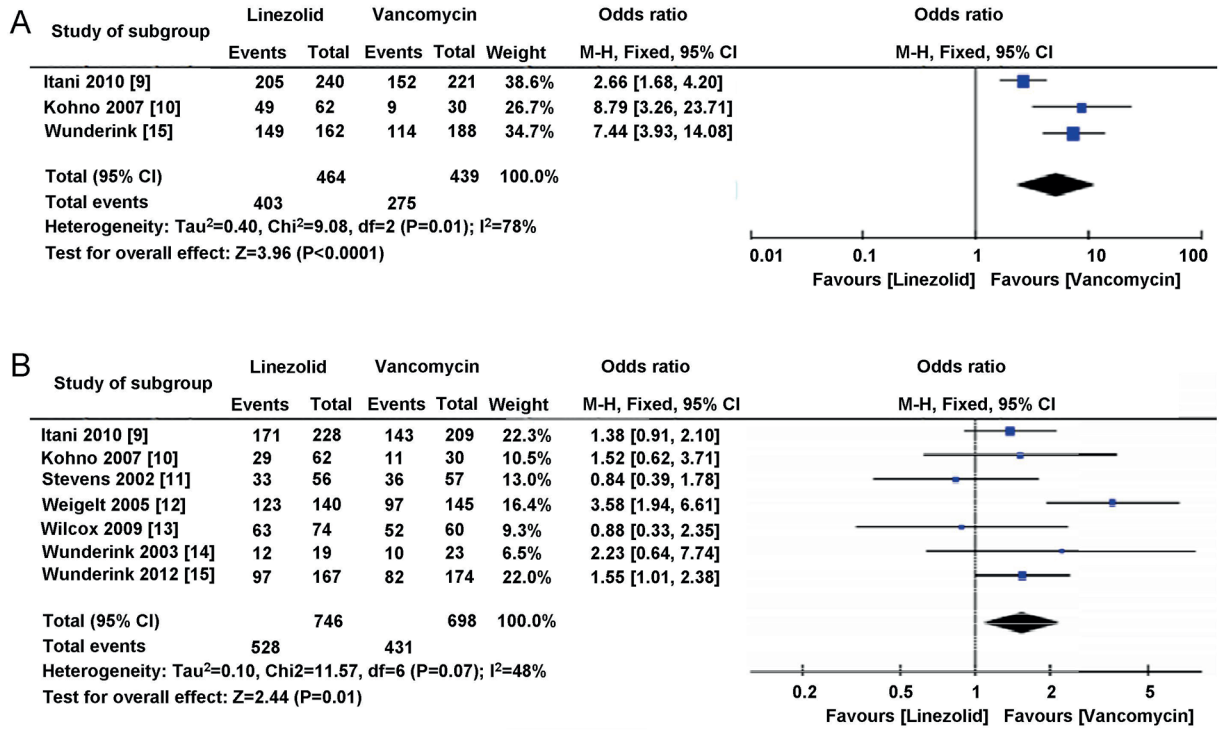

Figure 2. Forest plot of effect comparison between linezolid group and vancomycin group in MRSA clearance rate. A: The MRSA clearance rate. B: MRSA clearance rate of microbe-evaluable TOC patients. TOC: test of cure, MRSA: methicillin-resistant staphylococcus aureus.

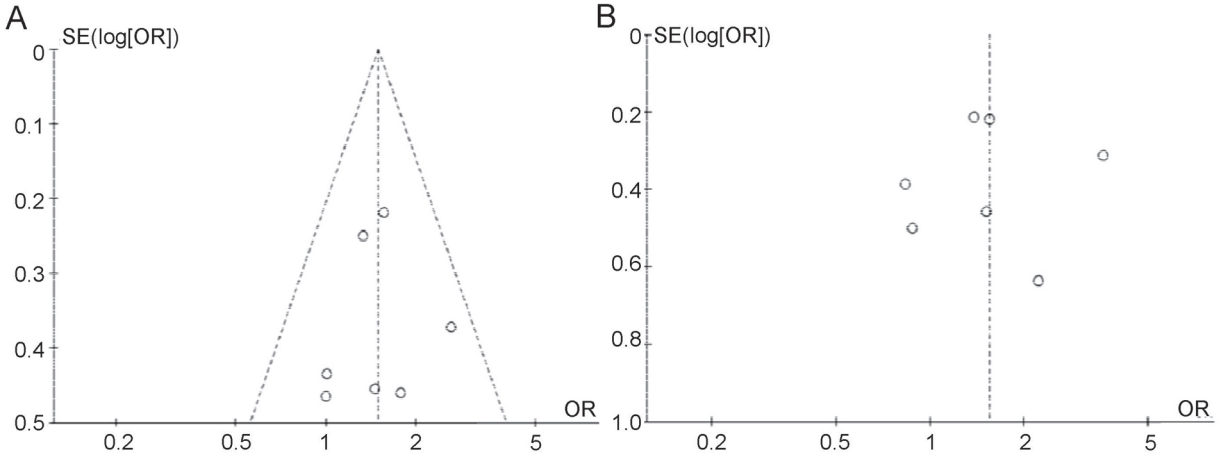

Figure 3. Funnel plot of publication bias analysis. ***A,*** Clinical cure rate; ***B,*** MRSA clearance rate. MRSA: methicillin-resistant staphylococcus aureus.

vancomycin in treating confirmed or suspected MRSA infections. The results showed that at the end of treatment and follow-up, the clinical efficacy and microbiological efficacy of linezolid group were better than vancomycin group. Our study has several limitations. Firstly, research with inadequate allocation concealment should be excluded from the analysis. In this meta-analysis, 7 studies did not mention allocation concealment method. Therefore, it may produce a selection bias. Secondly, the majority of included study did not mention the double-blind methods. Although the merger results were consistent with the original results, no blinded design may lead to overestimation. Therefore, there may be implementation bias in this study. Finally, there are some clinical heterogeneity among studies, which are likely to lead to different clinical outcomes and may affect the strength of meta-analysis and extrapolation of conclusions. In short, the meta-analysis showed that linezolid had better efficacy than vancomycinin for the treatment of MRSA-related infections. In addition, linezolid had other advantages, including no need to adjust dose in patients with renal insufficiency, oral formulation with 100% bioavailability, and no need to perform therapeutic drug monitoring. Therefore, compared with the classic glycopeptide antibiotics, its clinical application will be more extensive. However, it still should be used reasonably to avoid accelerating the generation and popularity of bacterial resistance. Also, the results may be limited by the flaws and potential bias of the analysis methods. Therefore, we should be cautious about the clinical significance of the conclusions of this meta-analysis. Definitive conclusions still need to be verified by higher-quality and more rigorously-designed head-to-head randomized controlled trials.

Conclusions

Based on the combined analysis of randomized controlled trials, the efficacy of linezolid should be better than that of vancomycin in the treatment of infections caused by MRSA, but the conclusions still need to be further validated by more well-designed RCTs of large sample.

Acknowledgments

This study was granted by the Chongqing Medical University Project (Grant No. XB0507) and National Key Clinical Nursing Project (Grant No. [2010] 305).

Conflict of interest

The authors declare no conflicts of interest.

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