Efficacy and safety of tigecycline doses for ventilator-associated pneumonia caused by multiple resistant bacteria: a systematic review and meta-analysis

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Abstract

Introduction: Ventilator-associated pneumonia (VAP) caused by multi-resistant bacteria is a serious complication in hospitalized patients. Tigecycline, a broad-spectrum antibiotic, has been suggested as a potential treatment option for this condition, but the optimal dose of tigecycline remains unclear. In this study, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of different doses of tigecycline in the treatment of VAP caused by multi-resistant bacteria.

Material and methods: To identify relevant studies, we conducted a comprehensive search of multiple databases including the Cochrane Library, Embase, PubMed, the Chinese biomedical literature database, CNKI, Chinese JP, and WP, covering the period up to December 2022. The search strategy was designed to identify studies that evaluated the efficacy and safety of different doses of tigecycline in the treatment of ventilator-associated pneumonia caused by multi-resistant bacteria. We assessed the quality of the included studies using the Jadad quality score, and performed a meta-analysis of the data using Stata software.

Results: Six articles, consisting of a total of 509 patients, were included, with 280 patients in the control group (low-dose tigecycline) and 229 in the observation group (high-dose tigecycline). There was no clinical heterogeneity or statistical heterogeneity between studies ($I^2 = 0\%$, $p = 0.80$), and a fixed-effect model was used to incorporate the effect size. The clinical effect of the observation group was significantly better than that of the control group (OR = 0.20, 95% CI: 0.13–0.30, $p < 0.001$). A meta-analysis of the adverse effects showed that there was no clinical heterogeneity or statistical heterogeneity between studies ($I^2 = 51\%$, $p = 0.10$), and a fixed-effect model was used to incorporate the effect size. The incidence of adverse effects in the observed group was similar to that of the control group (OR = 0.96, 95% CI: 0.61–1.50, $p = 0.85$).

Conclusions: Duration of high-dose tigecycline treatment for ventilator-related pneumonia caused by multi-resistant bacteria is associated with improved clinical efficacy without an increase in adverse effects. Therefore, it may offer a viable treatment option for patients with ventilator-related pneumonia caused by multi-resistant bacteria.

Key words: tigecycline, drug-resistant bacteria, ventilator-associated pneumonia, meta-analysis.

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Introduction

Critically ill patients often require respiratory treatment with a ventilator, but prolonged use of a ventilator may lead to ventilator-associated pneumonia (VAP). Ventilator-associated pneumonia is a leading cause of death in critically ill patients, with a mortality rate of 30–50% [1]. Common pathogenic bacteria associated with VAP include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudoquas aeruginosa*. Despite the efficacy of antibiotics in combatting bacterial infections, their extensive use has contributed to the emergence of progressively more drug-resistant strains, posing great challenges to the clinical treatment of ventilator-associated pneumonia [2]. Tigecycline is a glycyclin with superior antibacterial properties against Gram-negative bacilli, positive bacilli, and anaerobic bacteria [3]. However, with the increasing clinical application of tigecycline, many researchers have observed that the recommended dosage of tigecycline may be inadequate for the treatment of ventilator-related pneumonia caused by multi-resistant bacteria [4]. Further investigation into drug-resistant strains has revealed that high-dose tigecycline can significantly improve the clearance rate of multi-resistant bacteria and improve the treatment effect of ventilator-related pneumonia [5]. Accordingly, a thorough review of literature databases was conducted to investigate various doses of tigecycline for treating ventilator-associated pneumonia caused by multi-drug-resistant bacteria. A subsequent meta-analysis was performed to evaluate the efficacy and safety of high-dose tigecycline treatment for this condition. The results of this study aim to provide a theoretical foundation for the clinical management of patients with multidrug-resistant ventilator-associated pneumonia, and are presented as follows.

Material and methods

Literature search strategy

A systematic search was conducted in the Cochrane Library, Embase, PubMed, Chinese biomedical literature database, CNKI, literature retrieval in Chinese journal full text database, Wanfang, and web-based databases using a combination of keywords and free text. The Chinese search terms included "teacycline, different doses, ventilator-associated pneumonia", while the English search terms were "Tigacycline, Drug-resistant bacteria, and Ventilator-associated pneumonia". The search period for database construction was from inception until December 2022, and the search was conducted in both Chinese and English languages. The registration number is INPLASY 202340034. The DOI number is 10.37766/inplasy2023.4.0034.

Literature inclusion and exclusion criteria

(1) Inclusion criteria: 1. All the included studies are randomized controlled experiments. 2. The study subjects were patients with ventilator-associated pneumonia caused by multi-drug-resistant bacteria, and the indicators reflecting the clinical effect and safety were taken as the observation indicators (such as treatment effect, adverse effects, etc.). 3. The treatments involved include different doses of tigecycline, placebo, etc.

(2) Exclusion criteria: 1. Non-randomized controlled study. 2. Incomplete data in the article and repeated published literature. 3. Animal experiments, case reports, reviews, etc.

Data extraction and literature quality evaluation

The evaluation of literature quality was conducted using the literature evaluation criteria of the Cochrane System Evaluator Manual and the modified Jadad scale. In instances where there were divergent opinions, a third researcher was consulted to research a consensus. The modified Jadad scale score was based on randomized sequence generation, randomized concealment, blindness, and withdrawal criteria, with a score range of 1–3 representing low quality and 4–7 indicating high quality.

Statistical analysis

Statistical analysis was performed using Stata software. The included literature underwent heterogeneity testing using Cochran's Q test, with a statistical I^2 representation of > 50% or $p < 0.05$ indicating statistical heterogeneity among the literature. In the presence of statistical heterogeneity, the random effect model incorporated the effect size; conversely, the fixed effect model was employed. The weighted mean difference (WMD) and 95% confidence interval (95% CI) were used to represent the combined effect size of measurement data. RR and 95% CI were used for interval assessment of the combined effect size of counting data. Publication bias was assessed using a funnel plot and Egger's test, with the test level set at $\alpha = 0.05$.

Results

Basic characteristics of included literature

The initial step involved searching relevant databases for keywords related to the study title, followed by reviewing the abstracts of identified literature. Articles meeting the inclusion criteria were downloaded, and their content was thoroughly

assessed against the exclusion criteria. Ultimately, a total of 74 Chinese articles and 30 English articles were retrieved, and after careful examination, six articles were considered for analysis [6–11]. The literature screening flow chart is shown in Figure 1. The six included articles comprised 509 patients, with 280 in the control group and 229 in the observation group. The treatments employed in the studies included tigecycline and meropenem.

Basic characteristics of the literature included in Table I.

Meta-analysis results

Clinical efficacy

Clinical efficacy of different doses of tigecycline in patients with ventilator-associated pneumonia caused by multiple drug-resistant bacteria

The analysis included six articles that reported the clinical efficacy of different doses of tigecycline in patients with ventilator-associated pneumonia caused by multiple resistant bacteria. The meta-analysis revealed no clinical or statistical heterogeneity between studies ($I^2 = 0\%$, $p = 0.80$), and a fixed-effect model was used to determine the effect size. The clinical effect of the observation group was significantly better than that of the
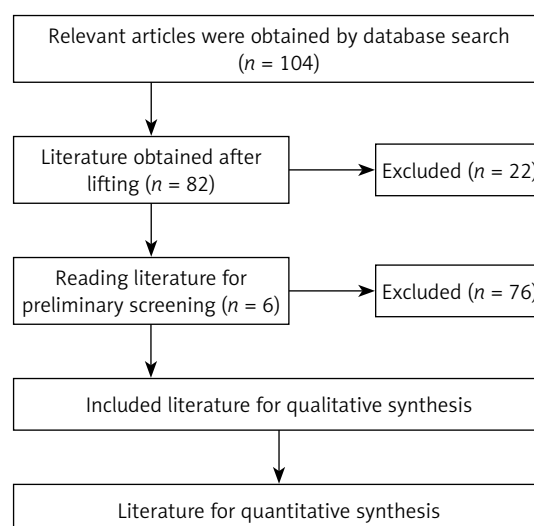

Figure 1. Process of literature screening

control group (OR = 0.20, 95% CI: 0.13–0.30, $p < 0.00001$), as shown in Figure 2.

Publication bias

Using a funnel plot and Egger's test, none of the six articles with clinical efficacy as an effect index were statistically significant ($p > 0.05$), suggesting no publication bias, as shown in Figure 3.

Table I. Basic characteristics

Order number	First author	Year of publication	Therapeutic method		Sample capacity	Outcome indicators	Jadad grade	Number of people	
			Control group	Observation group				Clinical effects	Un-toward effect
1	Feng Xianjun	2021	Tigecycline (first 100 mg, then 50 mg, 1/12 h)	Tigecycline (continued at 100 mg, 1 time/12 h)	30/38	Clinical efficacy and adverse reactions	6	14/29	8/11
2	Zou Yongyi	2020	Meropenem (1.0 g, 1 time/12 h)	Tigecycline (200 mg, 100 mg, 1/24 h)	50/50	Clinical efficacy and adverse reactions	6	35/48	12/4
3	Lou yi	2015	Tigecycline (first 100 mg, then 50 mg, 1/12 h)	Tigecycline (continued at 100 mg, 1 time/12 h)	35/29	Clinical efficacy and adverse reactions	5	17/24	12/14
4	Fei Min	2016	Tigecycline (50 mg, once/12 h)	Tigecycline (100 mg, once/12 h)	31/40	Clinical efficacy and adverse reactions	5	10/24	0/0
5	Zang Huiling	2018	Meropenem (1.0 g, 1 time/8 h)	Tigecycline (200 mg, 100 mg, 1/12 h)	28/21	Clinical efficacy and adverse reactions	5	10/16	0/0
6	Xia G	2020	Tigecycline (first 100 mg, then 50 mg, 1/12 h)	Tigecycline (200 mg, 100 mg, 1/12 h)	106/51	Clinical efficacy and adverse reactions	6	30/36	43/24

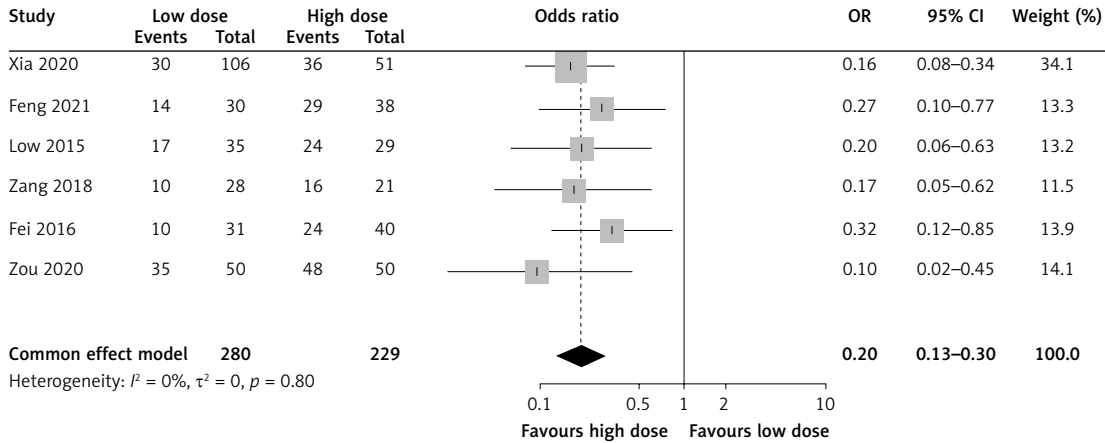Changwen Feng, Xiaoshan Yang, Junlin Lu, Qingming Mo, Zhaoxu Cai, Wendian Zhu

Figure 2. Forest plot of the clinical efficacy of different doses of tigecycline in patients with ventilator-associated pneumonia caused by multiple resistant bacteria
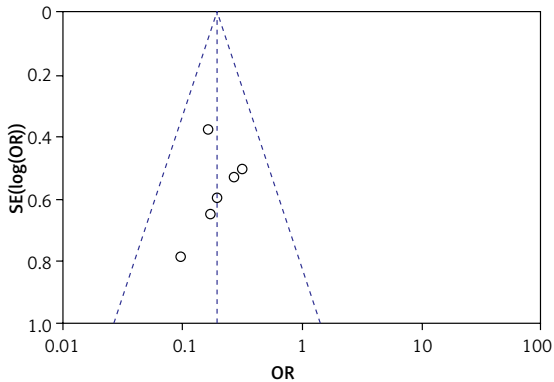

Figure 3. Funnel plot of the clinical efficacy of different doses of tigecycline in patients with ventilator-associated pneumonia caused by multiple drug-resistant bacteria

Adverse reactions

Adverse effects of different doses of tigecycline treatment in patients with ventilator-associated pneumonia caused by multiple drug-resistant bacteria

A total of 6 articles reported the adverse effects of tigecycline in patients with ventilator-associated pneumonia caused by different doses of multiple resistant bacteria. The meta-analysis revealed

no clinical heterogeneity or statistical heterogeneity between the included studies (I^2 = 51%, p = 0.10). The effect size was incorporated using a fixed-effect model, indicating that the incidence of adverse effects in the observed group was similar to that of the control group (OR = 0.96, 95% CI: 0.61–1.50, p = 0.85), as shown in Figure 4.

Publication bias

Using a funnel plot and Egger's test, none of the four articles with adverse effects as effect indicator were statistically significant (p > 0.05), suggesting no publication bias, as shown in Figure 5.

Discussion

Ventilator-related pneumonia is a prevalent clinical condition that usually occurs in respiratory critical care units. Reports indicate that gland-negative bacteria account for a significant proportion of these cases, with the trend increasing annually. Additionally, with the extensive use of clinical antibiotics, the prevalence of multi-drug-resistant strains is also on the rise. Therefore, the treatment of ventilator-associated pneumonia resulting from multi-drug-resistant bacteria has become a challenging issue in clinical practice.
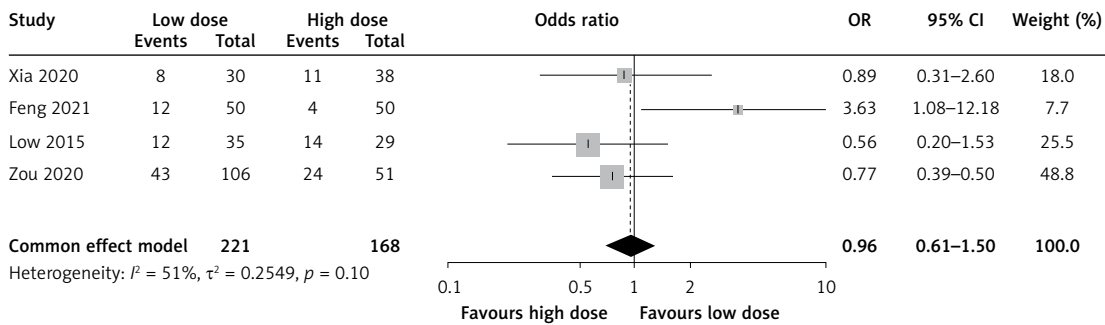

Figure 4. Forest plot of adverse reactions in patients with ventilator-associated pneumonia caused by different doses of tigecycline
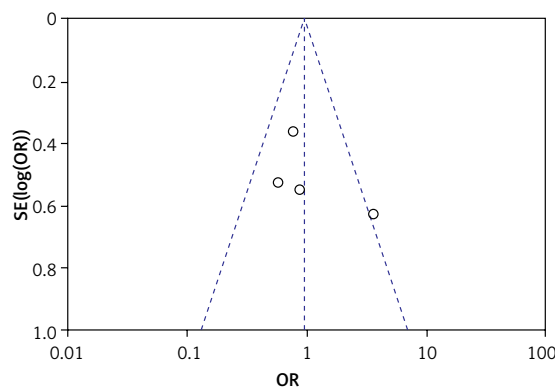
Figure 5. Funnel plot of adverse reactions in patients with ventilator-associated pneumonia caused by various doses of tigecycline

Tigecycline is an antibiotic that exhibits a broad antibacterial spectrum and has been shown to be effective against multiple resistant bacteria. However, the conventional doses of tigecycline (maintenance dose at 50 mg, once every 12 h) have limited efficacy in treating ventilator-related pneumonia caused by multi-resistant bacteria. This is due to the low strain clearance rate and extended drug use time and hospitalization duration. On the other hand, high-dose tigecycline (maintenance dose at 100 mg, once every 12 h) has demonstrated certain advantages over conventional doses in treating multiresistant bacteria. Nevertheless, clinical scholars are concerned whether high-dose tigecycline treatment would cause more serious adverse reactions. Therefore, to further understand the treatment efficacy and safety of different doses of tigecycline in treating patients with multi-resistant bacteria, a meta-analysis was conducted. Six articles, including five in Chinese, were selected according to the inclusion and exclusion criteria. The meta-analysis revealed that high-dose tigecycline was significantly more effective than the control group in treating patients with multi-resistant pneumonia (OR = 0.20, 95% CI: 0.13–0.30, $p < 0.00001$). The results suggest that high doses of tigecycline in patients with multi-resistant bacteria are more effective, and can effectively improve the therapeutic effect. Safety is also a key concern for clinicians, and the meta-analysis showed that the incidence of adverse reactions in the observed group did not differ from the control group (OR = 0.96, 95% CI: 0.61–1.50, $p = 0.85$). The results suggest that high doses of tigecycline do not increase the incidence of adverse effects.

The study has the following limitations. The lack of specific method descriptions regarding random sequence generation, no mention of allocation concealment, and no double-blinding in the included studies may lead to bias in selection, implementation, and detection, and can lead to false-positive results. Second, the included studies were all single-center studies, with small sample sizes and varying lengths of interventions, which may lead to large differences in results. Third, this study only compared the differences between low-dose and high-dose tigecycline treatment, but the dose was inconsistent between different studies [12–20].

In conclusion, high-dose tigecycline for multi-resistant bacteria has better clinical efficacy without an increase in adverse effects. Therefore, it may offer a viable clinical treatment for patients with ventilator-associated pneumonia caused by multi-resistant bacteria.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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