Pakistan J. Zool., pp 1-6, 2023. **DOI**: https://dx.doi.org/10.17582/journal.pjz/20230524050529

Efficacy of Amikacin Combined with Piperacillin/Tazobactam Sodium in Elderly with Severe Drug-Resistant *Pseudomonas aeruginosa* Pneumonia

Hongxiao Li[1]*, Xiying Wu[2], Dengxiang Wu[1] and Jiangqing Yu[1]

[1]Department of Respiratory and Critical Care Medicine, The Second Peoples Hospital of Jingdezhen, Jingdezhen 333000, Jiangxi Province, China
[2]Department of Oncology, The Second Peoples Hospital of Jingdezhen, Jingdezhen 333000, Jiangxi Province, China

Article Information
Received 24 May 2023
Revised 28 May 2023
Accepted 08 June 2023
Available online 27 July 2023
(early access)

Authors' Contribution
HL and XW conducted the experiments in this study. DW and JY contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Amikacin, Piperacillin/tazobactam sodium, Drug-resistant Pseudomonas aeruginosa, Pneumonia

ABSTRACT

The purpose of this study was to demonstrate the effects of amikacin combined with piperacillin/tazobactam sodium (PPC/TS) in the therapy of severe resistant *Pseudomonas aeruginosa* (*Pa*) pneumonia in elderly individuals. The sample of 50 elderly patients with *PA* pneumonia were selected and assigned into control group (Ctrl group, n=25, PPC/TS treatment) and experimental group (Exp group, n=25, amikacin +PPC/TS treatment) according to the single and even numbers. The between-group differences in CURB-65 score, CPIS score, APACHE II score, SOFA score, infection-related indicators, and bacterial clearance were compared. The CURB-65, CPIS, APACHE II, and SOFA scores in both groups were greatly decreased after the treatment, and the scores in the Exp. group were inferior to those in the Ctrl group substantially (P<0.05). The levels of WBC, NEUT, PCT, CRP, IL-6, and HBP in both groups were decreased drastically, and the scores in the Exp. group were dramatically lower than those in the Ctrl group (P<0.05). The bacterial clearance rate in the Exp. group was 64%, which was notably superior to 28% in the Ctrl group (P<0.05). The combination of amikacin and PPC/TS can greatly enhance the disease severity in elderly patients with severe drug-resistant *PA*, control the in vivo inflammatory response, promote the recovery of patients, enhance the quality of life of patients, and enhance the prognosis of the disease, which can provide a reference for clinical application.

INTRODUCTION

Pneumonia is the most common lower respiratory tract infectious disease. Statistics show that approximately one-fifth of children need to be in the intensive care unit, and one-third of children need mechanical ventilation. Compared with elderly individuals, their incidence rate and risk of death due to pneumonia are several orders of magnitude higher than those of children (Schöll and Rohde, 2019). Severe pneumonia, also an extreme case of pulmonary infection, is a severe respiratory disease in the clinic with rapid progression and high mortality (Wang *et al*., 2022). In addition, elderly patients have weak immunity, relatively more basic diseases, and insufficient ability to resist disease invasion, making them the most common population with drug-resistant bacterial infection. Among drug-resistant bacterial infections such as pneumonia, gram-negative (G) bacilli such as *Pseudomonas aeruginosa* (*Pa*) account for the majority (Jarjees, 2020). *Pa* has the characteristics of strong drug resistance and complex drug resistance mechanisms. Nevertheless, with the excessive use of antimicrobial agents, the drug resistance of bacteria has become increasingly serious, and multidrug-resistant and multidrug-resistant gram-negative bacteria are increasing each year, which brings great difficulties and challenges to clinical anti-infection treatment (Baer *et al*., 2018). The research and development of new antibiotics is difficult, the cost investment is large, the cycle is long, and the clinical demand has not been met. All these factors have brought great challenges to clinically effective anti-infection treatment and have become a great hidden danger that threatens the life and health of patients, especially

* Corresponding author: zhongduzi224677615@163.com
0030-9923/2023/0001-0001 $ 9.00/0

elderly patients. Nevertheless, the drug resistance rate of some old antibacterial drugs is greatly reduced because they have not been utilized clinically for a long time. Nevertheless, if they are appropriately applied clinically, they have a favorable effect on drug-resistant bacteria with few side effects (Taherikalani *et al*., 2013). Hence, the strategy of alternating and recycling the use of antibiotics and the new use of old drugs has been proposed by some experts and has come into the view of clinicians.

Amikacin was limited in its use in the 1990s due to its renal toxicity. Nevertheless, it can be utilized appropriately in the therapy of severe infection and monitors the blood concentration, renal function, and hearing of patients during use. At the same time, single daily dose administration and individualized administration to patients can reduce renal toxicity (Dong-Jin *et al*., 2019). A recent *in vivo* study suggested that amikacin, compared with meropenem, cefepime, ceftazidime, and ciprofloxacin, had a higher sensitivity to *Pa*, a lower minimum inhibitory concentration, and the least resistance to *Pa* (Avent *et al*., 2022). The sensitivity of amikacin is not only related to its low clinical use frequency but also depends on its unique structure. Only one site in its molecular structure is sensitive to aminoglycoside inactivating enzymes, while gentamicin and tobramycin have six sites. In addition, two or more aminoglycoside-modifying enzymes need to act on amikacin at the same time to form resistance to *PA* (Wang *et al*., 2022). Piperacillin/tazobactam sodium (PPC/TS) is an antibacterial drug containing enzyme inhibitors, is a compound preparation of PPC and tazobactam, and is a broad-spectrum antibacterial drug. The antibacterial spectrum covers gram-positive bacteria, gram-negative bacteria, anaerobic bacteria, and enterococci. PCP/TS has good antibacterial activity against *K. pneumoniae, E. coli*, and *Pa* (Casimir-Brown *et al*., 2021).

Nevertheless, to date, there are few studies on the treatment of elderly patients with severe drug-resistant *Pa* with the combination of amikacin and PPC/TS, so in this study, elderly patients with severe drug-resistant *Pa* were recruited to expound the adoption effect of the combination of these two drugs in its treatment to provide a reference for the selection of antibacterial regimens in clinical adoption in the future.

MATERIALS AND METHODS

Subjects

Hospitalized patients in the ICU of our hospital from May 2020 to May 2022 were recruited. According to the inclusion and exclusion criteria, 50 elderly patients with *Pa* pneumonia were finally determined and rolled into control (Ctrl) group (25 cases, PPC/TS treatment) and experimental (Exp) group (25 cases, amikacin +PPC/TS treatment) according to the single and even numbers of collected data.

Elderly patients in both groups were eligible to join the study if they met the following inclusion criteria: (1) aged ≥65 years old, (2) main criteria: (i) mechanical ventilation was needed, (ii) patients with septic shock need vasoactive drugs; secondary criteria. (i) multiple lobar infiltration, (ii) PaO2/FiO2≤250, (iii) respiratory frequency>30 times/min, (iv) hyperuricemia (urea nitrogen ≥20 mg/dl or 7 mmol/L), (v) vague consciousness and disorientation, (vi) white blood cell (WBC) count<4×109/L, (vii) thrombocytopenia, platelet count<100×109L, (viii) hypothermia, with body temperature < 36.0°C, Included subjects should meet one major criterion or three secondary criteria. (3) patients diagnosed with PA infection by etiological diagnosis. (4) the patient gave informed consent and signed the informed consent voluntarily.

Elderly patients who utilized immunosuppressive agents or cytotoxic drugs, sputum culture susceptibility test results showed resistance to amikacin or PPC/TS, patients with lung diseases such as tuberculosis and lung tumor, and patients with severe cardiac function, liver dysfunction, and immune dysfunction were excluded from the study.

Efficacy evaluation indexes

The treatment effect was evaluated before treatment and two weeks after treatment. The evaluation indicators in this study mainly included the following.

(1) Pulmonary severity "confusion, uremia, respiratory rate, blood pressure, and age over 65 years" (CURB-65) score (Patel, 2021) was calculated. The change in CURB-65 score was assessed before and after treatment. The higher the score, the more severe the illness and the greater the risk. There were five indicators in total, and one score was gained if one was met: (i) patients with consciousness impairment, (ii) urea nitrogen > 7 mmol/L, (iii) respiratory frequency ≥30 times/min, (iv) systolic blood pressure<90 mmHg, (v) age ≥65 years old. Score of 0-1 was the low-risk group (mild), or no sepsis patients; scores of 2 were middle-risk group, patients with sepsis; scores of 4-5 were high-risk group, patients with severe sepsis or septic shock.

(2) Clinical pulmonary infection score (CPIS) (Sathitakorn *et al*., 2022) scores were assessed before and after treatment. The score ranged from 0 to 12 points. The higher the score was, the higher the risk of death.

(3) Acute physiological and chronic health score (APACHE II) (Andrade *et al*., 2022) scores were assessed before and after treatment, including the acute physiological score (APS) of 12 items, age score and chronic health score. The higher the score was, the worse

the prognosis.

(4) Sepsis-related organ failure assessment (SOFA) (Pölkki *et al*., 2022) score covers six organ systems, including the respiratory system, circulatory system, liver system, blood system, kidney system, and central nervous system. The worst score was recorded every day. The higher the score, the more serious the disease became.

(5) Determination indicators of infectious efficacy were as follows. The levels of change in WBC, neutrophil (NEUT), procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), and heparin binding protein (HBP) indicators of patients in the two groups before and after the treatment were compared.

(6) Determination of etiological efficacy Bacterial clearance was observed in both groups before and after treatment. The criteria for evaluation and calculation of bacterial clearance were determined by referring to guiding principles for clinical research on antibacterial drugs (Chang *et al*., 2019).

Statistical analyses

Using, SPSS 23.0, Meañ±SEM represented measurement data in accordance with the normal distribution, mild skewed distribution, and homogeneity of variance. Independent sample *t* tests were used for comparisons between two groups. Data within the same group were compared, and a *t* test was applied to paired samples. A nonparametric test was adopted for nonconformance. The chi-square test was adopted for enumeration data, and the nonparametric test (rank sum test) was for comparison of rank data. $P<0.05$ indicated that there was a significant difference.

RESULTS

Before treatment, CURB-65, CPIS, APACHE II, and SOFA scores demonstrated inconsiderable between-group differences ($P>0.05$). After the treatment, patients in the Exp. group had CURB-65 score of 1.4±0.5, CPIS score of 2.7±0.9, APACHE II score of 12.6±3.2, and SOFA score of 3.1±1.8, while those in the Ctrl group had CURB-65 score of 2.7±0.7, CPIS score of 4.4±1.3, APACHE II score of 15.1±3.7, and SOFA score of 4.7±2.1. Relative to those before the treatment, the differences were marked ($P<0.05$), and the scores of the Exp. groups were inferior to the Ctrl group ($P<0.05$) (Fig. 1).

Before the treatment, slight between-group difference was found in WBC, NEUT, PCT, CRP, IL-6, and HBP levels ($P>0.05$). After the treatment, patients in the Exp. group had WBC of (10.5±1.7)×10^9/L, NEUT of (66.2±2.8)%, PCT of (1.7±0.5) ng/mL, CRP of (33.9±2.6) mg/L, IL-6 of (52.8±3.5) pg/mL, and HBP of (106±2.4) ng/mL. Patients in the Ctrl group had WBC of (12.4±1.2)×10^9/L, NEUT of (73.9±3.1)%, PCT of (2.6±0.4) ng/mL, CRP of (58.3±3.2) mg/L, IL-6 of (67.4±3.1) pg/mL, and HBP of (16.3±3 3.8) ng/mL. All indicators in both groups were greatly enhanced after the treatment ($P<0.05$), and all indicators in the Exp. group were markedly inferior to the Ctrl group (Fig. 2).

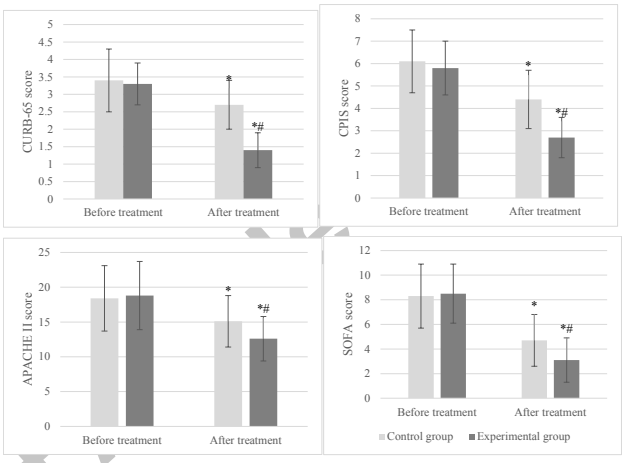

Fig. 1. Effect of amikacin + Pipercillion on the CURB-65, CPIS, APACHE II and SOFA scores of elderly patient. *$P<0.05$ vs. before treatment; # $P<0.05$ vs. Ctrl group; * and # had the same meanings for all figures.

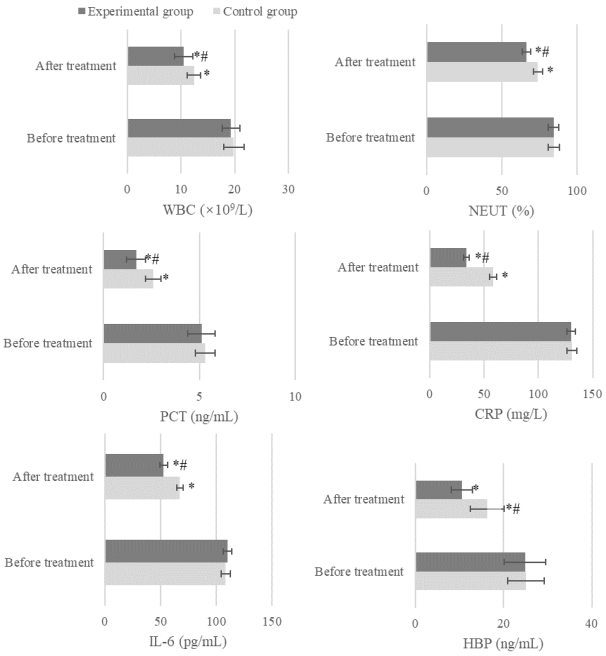

Fig. 2. Effect of amikacin + pipercillion on WBC, NEUt, PCT, CRP, IL-6 and HBP pf patients before and after infection.

Partial and complete bacterial clearance were classified as bacterial clearance. The results showed that the bacterial clearance rate of patients in the Exp. group was 64% (16 cases), which was drastically superior to the 28% (7 cases) of patients in the Ctrl group ($P < 0.05$) (Fig. 3).

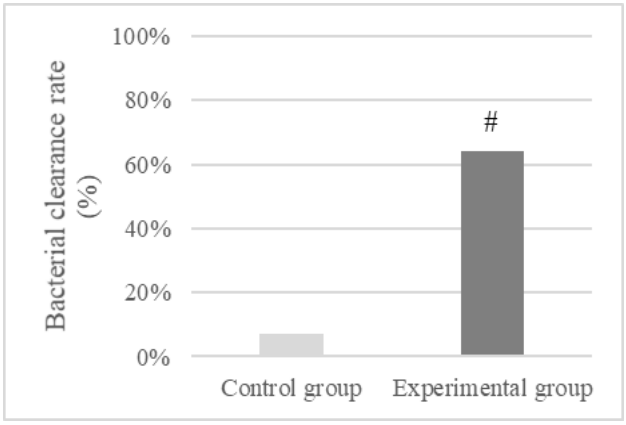

Fig. 3. Comparison of bacterial clearance rates.

DISCUSSION

Severe pneumonia has a high mortality rate in lower respiratory tract infection, mainly because the progression of the disease will affect the whole-body organs and then develop into sepsis and even septic shock, so early treatment with broad-spectrum antibacterial drugs is particularly crucial (Schweitzer *et al*., 2022). *Pa* is one of the common bacteria causing infectious diseases, and it commonly colonizes patients with low immune function and a variety of basic diseases in the hospital. Most elderly patients in the ICU have a long disease course, attach importance to the disease and many basic diseases, so their immune function is relatively weak, resulting in the decline of respiratory tract defense function, and become the prone population of *Pa* pneumonia. Second, most of the inpatients in the ICU have the characteristics of a relatively long course of disease, basic diseases often involving multisystem medication, and invasive operation during hospitalization. The longer the patient is hospitalized, the greater the risk of infection (Long *et al*., 2020). With continuous changes in bacterial resistance mechanisms, conventional treatment for elderly patients with severe *Pa* has poor clinical efficacy, and bacterial resistance is becoming increasingly serious. In this study, the combination of amikacin and PPC/TS was adopted in the therapy of elderly patients with severe drug-resistant *Pa* to observe the therapeutic effect to provide a reference for the selection of clinical treatment options.

The results suggested that in contrast to the scores before treatment, the CURB-65, CPIS, APACHE II, and SOFA scores of patients in the two groups were drastically decreased, and the scores in Exp group were substantially lower than those in Ctrl group ($P<0.05$). The CURB-65 score, covering respiratory, renal, circulatory, and neurological aspects, is a reliable indicator for evaluating the severity of pneumonia. Moreover, it is simple to operate and has good prediction sensitivity (Preti *et al*., 2022). This study suggested that the combination of amikacin and PPC/TS was beneficial for improving the severity of the patient's condition. The CPIS scoring system included body temperature, secretion amount, oxygenation index, imaging examination, and etiology detection, which could be applied to analyze and judge the severity of pulmonary infection and was significant for guiding the cure rate of the trial (Shen *et al*., 2019). It was verified that the combination of amikacin and PPC/TS was beneficial for the recovery of infection in our patient. The APACHE II score is currently a critical illness assessment system widely utilized in clinical practice that can accurately estimate the disease severity and prognosis of critically ill patients (Asai *et al*., 2021). This study found that the combination of amikacin and PPC/TS is conducive to improving the prognosis and quality of life of patients. The SOFA scoring system is currently a popular scoring system for clinical adoption to evaluate the condition and prognosis of critically ill patients (Macichová *et al*., 2020). The combination of amikacin and PPC/TS is conducive to reducing the extent of damage to organ function in patients and improving clinical prognosis.

Later, infection-related indicators were selected for evaluation. The results suggested that after treatment, the levels of WBC, NEUT, PCT, CRP, IL-6, and HBP in the two groups were decreased, and all indicators in Exp group were inferior to Ctrl group ($P<0.05$). This indicates that the combination of amikacin and PPC/TS has a positive effect on the control of the inflammatory response, which is greatly superior to the use of PPC/TS drugs alone. A study also suggested that the combination of ceftazidime/avibactam and amikacin had the potential to treat drug-resistant *Pa* (Mikhail *et al*., 2019). Based on treatment with cefoperazone sodium /sulbactam sodium, Wang *et al*. (2021) applied PPC sodium/TS to treat elderly patients with respiratory tract infection and found that the serum levels of PCT, CRP, WBC, and NEUT of patients were lower than those before treatment. These results are consistent with our results in this study. Nevertheless, some scholars do not support the use of inhaled amikacin as an adjuvant treatment to standard treatment in patients with gram-negative pneumonia after mechanical ventilation (Niederman *et al*., 2020). Finally, it was found that the

bacterial clearance rate in Exp group was superior to Ctrl group ($P < 0.05$), indicating that the combination of amikacin and PPC/TS was conducive to the removal of bacteria and to enhance the etiology-related efficacy.

The results indicated that relative to traditional symptomatic support therapy in western medicine, the combination of amikacin and PPC/TS could significantly enhance the disease severity of elderly patients with severe drug-resistant *Pa*, control the *in vivo* inflammatory response, delay the further development of the disease, enhance the bacteriological efficacy, and enhance the therapeutic effect, with clinical adoption value. Nevertheless, the sample size that can be included this time is small, and systematic bias is inevitable in selection, which needs multicenter and multisampling supplementation to further verify.

CONCLUSION

The results suggested that the combination of amikacin and PPC/TS could notably enhance the disease severity of elderly patients with severe drug-resistant *PA*, control the *in vivo* inflammatory response, promote the recovery of patients, enhance the quality of life of patients, and enhance the prognosis of diseases relative to traditional symptomatic support treatment in Western medicine, which could provide a reference for clinical application. Nevertheless, the sample size that can be included this time is small, and systematic bias in selection is inevitable. Moreover, due to the limited research time and conclusion, multicenter and multisample supplementation is required for further verification.

Funding

Not applicable.

IRB approval

This study was approved by the Advanced Studies Research Board of the Second People' s Hospital of Jingdezhen, Jingdezhen 333000, Jiangxi Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of The Second People' s Hospital of Jingdezhen, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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