A Prospective Trial of Nebulized Amikacin in the Treatment of Bronchiectasis Exacerbation

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Keywords

Bronchiectasis · *Pseudomonas aeruginosa* · Bacteria eradication rate · Nebulized amikacin treatment

Abstract

Background: *Pseudomonas aeruginosa* is the most common pathogenic bacteria in bronchiectasis (BE) patients. The availability and security of nebulized amikacin treatment are unknown. **Objective:** The purpose of this study was to explore the efficiency and adverse effects of nebulized amikacin treatment for 2 weeks, administered as intravenous therapy during exacerbation of BE patients infected with *P. aeruginosa*. **Methods:** A total of 143 patients with exacerbation of BE were screened between January 2013 and March 2016 at five tertiary hospitals in Shandong Province, China. The BE patients were diagnosed by high-resolution computed tomography scans, and all of them were confirmed to be infected with *P. aeruginosa* after sputum culture test. Seventy-four patients were assigned to the intervention group and received amikacin nebulization (0.2 g) treatment twice daily for 2 weeks along with intravenous antibiotic therapy. Sixty-nine patients were assigned to the control group and received standard antibiotic therapy alone. The primary out-

come was the rate of bacterial eradication from the sputum, and the secondary outcomes were drug resistance and adverse effects. **Results:** The bacterial eradication rate of sputum in the intervention group (51.4%) was significantly higher compared to that in the control group (23.2%) ($\chi^2 = 14.211$, $p = 0.030$). Drug sensitivity testing showed that there were 5 drug-resistant cases in the intervention group and 7 in the control group, which was not significantly different. Three patients dropped out of the trial due to adverse effects. None of the patients had renal injury. **Conclusions:** Nebulized amikacin treatment is a safe treatment for exacerbation of BE and significantly increases the bacterial eradication rate of sputum.

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Introduction

Bronchiectasis (BE) is characterized by persistent airway damage, bronchi dilatation, and recurrent bacterial infections [1]. *Pseudomonas aeruginosa* is the most common pathogenic bacteria in BE patients, and the life expectancy of patients infected with *P. aeruginosa* is significantly reduced. Relevant data displayed that 49.0% of BE

patients had *P. aeruginosa* cultured from their sputum on at least one occasion. The mortality of patients with *P. aeruginosa* ranged from 7.7% at 1 year to 13.6% at 2 years to 30–50% at 5 years. Thus, treatment and eradication of *P. aeruginosa* infection is essential [2, 3].

Intravenous antibiotic therapy is an essential method to control airway infection in BE patients. However, due to the low drug concentration reaching the alveoli, the eradication rate of bacteria is very low. Tobramycin and liposomal ciprofloxacin inhalation have some beneficial effects on BE [4, 5]. Amikacin also has some advantages, such as minor local irritation, low price, and high sensitivity to *P. aeruginosa*, and can be used for nebulized therapy [6]. One study demonstrated that nebulized amikacin liposomes have some beneficial effects on BE; however, there is still a long road before amikacin can be applied to clinical therapy [7]. In this study, we aimed to determine the efficiency and adverse effects of nebulized amikacin treatment for 2 weeks along with intravenous antibiotic therapy.

Patients and Methods

Patients

This study was a randomized, prospective, multicenter clinical trial. Written informed consent was obtained from each patient prior to randomization. Eligible patients were screened and randomized between January 2013 and March 2016 at five tertiary hospitals in Shandong Province, China. One hundred and fifty-two patients (60 male, 92 female; age range 18–75 years) were diagnosed with high-resolution computed tomography scans. The inclusion criteria included BE (idiopathic or postinfectious) [8, 9], nonsmokers and former smokers, pulmonary function test results showing forced expiratory volume in 1 s (FEV₁) ≥30% predicted value, *P. aeruginosa* infection verified by sputum culture test, and *P. aeruginosa* sensitivity to amikacin. The exclusion criteria included comorbidities, such as diabetes mellitus, cancer, serious heart and liver diseases, active tuberculosis, or renal failure. Patients allergic to amikacin were also excluded. The excluded etiologies included allergic bronchopulmonary aspergillosis, primary ciliary dyskinesia, pulmonary fibrosis, rheumatism, and immunodeficiency. Patients who could not tolerate nebulized amikacin therapy and had bronchospasm or dyspnea were classified as suffering adverse effects and excluded.

Interventions

The intervention group received nebulized amikacin sulfate twice daily by jet atomizer. Amikacin sulfate (2 mL of 0.2 g/mL) was added into 3 mL normal saline, resulting in a final solution with a pH of 6.0 and an osmolality of 281 mOsm/L. The control group received nebulized normal saline (5 mL) twice daily by jet atomizer which had a pH of 7.0 and an osmolality of 280 mOsm/L.

Both the control group and the intervention group received one or two of four sensitive antibiotics according to the results of the drug resistance test. The physician in charge made a decision

regarding the selection of the antibiotic that was used for 2 weeks, according to the Spanish consensus on the prevention and treatment of *P. aeruginosa* bronchial infections in cystic fibrosis (CF) patients [10]. The recommended antibiotics included meropenem, cefoperazone sodium/sulbactam sodium, ciprofloxacin or levofloxacin, and piperacillin or tazobactam. Once pulmonary function test results suggested that either obstructive or mixed ventilation function disturbance was present, inhalation of Bricanyl (2.5 mg) twice daily was applied. The use of other expectorants or bronchodilators was decided by the physician in charge.

Indexes

Each of the indexes below was tested before the start of therapy and after 14 days of treatment. The primary indexes included bacterial properties of the sputum, including eradication rate, persistence, replacement, and reinfection. The bacterial eradication rate of the sputum was calculated by the number of *P. aeruginosa*-eradicated cases according to sputum culture testing result [11]. Sputum samples were collected in the morning after toothbrushing and gargling, before the patients used any medicine. Eligible sputum samples were defined as having ≥25 white blood cells/high-power field and ≤10 epithelial cells/high-power field; the samples were sent for testing within 60 min. Sputum samples were collected again after 14 days. If the second sputum culture test showed a negative result after the first one had been positive, it was defined as eradicated. A positive *P. aeruginosa* result, as before, was defined as persistence. New pathogenic bacteria occurrence without any clinical symptoms was defined as replacement, and having infectious symptoms was defined as reinfection [11]. Secondary indexes included the patient's total sputum weight (collected over 24 h) and sputum property score. The sputum properties were graded from 1 to 4, with 1 being assigned to transparent mucous sputum, 2 to yellow purulent sputum, 3 to green purulent sputum, and 4 to black green purulent sputum [12]. Additionally, the degree of dyspnea was assessed by the modified Medical Research Council (mMRC) scale established by the British Medical Association [13]. The patient's quality of life was assessed by the COPD Assessment Test (CAT) score [14].

Pulmonary function tests were performed before therapy, repeated three times, and the maximum value was used for analysis. Following treatment, pulmonary function tests were reviewed for forced vital capacity (FVC), FEV₁, FEV₁/FVC ratio (FEV₁/FVC), etc. Antibiotic resistance tests were applied in eligible sputum samples using a microdilution method or a disk diffusion method as recommended by the National Committee for Clinical Laboratory Standards. The results of the drug resistance tests of sputum bacteria before and after therapy were compared to assess the change in drug resistance.

Adverse effects after inhalation therapy were recorded, including cough, dyspnea, increasing rhonchus, decreasing level of audition or tinnitus, etc.

To test renal function, blood urea nitrogen and creatinine levels were measured in peripheral blood before and after therapy.

Statistical Analysis

All analyses were conducted with the Statistical Package for the Social Sciences (SPSS) software, version 19.0. Measurement data were expressed as mean ± standard deviation and analyzed using the Student *t* test. The χ^2 test was applied to compare qualitative data. A *p* value <0.05 was considered statistically significant.

Fig. 1. Assessment, randomization, and follow-up of patients with exacerbation of bronchiectasis.

Results

Study Population

The study procedure is shown in Figure 1. A total of 178 patients were screened in this study, and 26 unqualified patients (14.6%) were excluded. The remaining 152 patients were randomly assigned to two groups: 79 patients to the intervention group with nebulized amikacin and 73 patients to the control group. Nine patients were excluded from the final analysis due to dropout, 5 in the intervention group (6.3%) and 4 in the control group (5.6%). The patients' baseline characteristics are listed in Table 1. All screened patients who underwent randomization had never received nebulized amikacin therapy previously. Finally, 74 patients were in the intervention group (93.7%) and 69 in the control group (94.5%). When the two groups were compared, the baseline characteristics showed no significant differences in sex, age, smoking history, mMRC score, CAT score, sputum weight, sputum properties score, classification of BE, lung CT, or pulmonary function. Additionally, drug usage was not significantly different between the two groups (Table 2).

Microbiology Analysis

The results of microbiological analysis suggested a significant difference in sputum bacterial eradication rate between the intervention group (38/74, 51.4%) and the control group (16/69, 23.2%) (Table 3). Drug resistance tests showed that 5 patients developed drug resistance in

the intervention group whereas 7 patients developed drug resistance in the control group.

Dyspnea and Quality of Life Analysis

The level of dyspnea (mMRC score) and quality of life (CAT score) showed no significant difference between the two groups. However, the mMRC and CAT scores showed significant differences before and after treatment in both groups. Sputum weight decreased, and the sputum properties score was improved in both groups following therapy (Table 4).

Pulmonary Function Test

All indexes of the pulmonary function test showed no significant differences before and after therapy in the control and the intervention group (Table 4).

Adverse Effects

In the intervention group, 3 patients were excluded. Two patients (4%) experienced bronchospasms. One patient experienced nausea and developed dyspnea and stridor, which was relieved by the inhalation of bronchodilators. Five patients experienced bucking at the time of inhalation, but all patients tolerated the therapy. In the control group, 3 patients (4%) experienced bucking, and 1 patient was excluded due to bronchospasm. Loss of hearing or development of tinnitus did not occur in either group. Blood urea nitrogen and creatinine levels in peripheral blood did not change before and after nebulization in both groups.

Table 1. Baseline characteristics of the study patients

	Total (n = 143)	Intervention group (n = 74)	Control group (n = 69)	p value
Male	60 (42.0%)	28 (40.6%)	32 (43.2%)	0.87
Age, years	56.9±11.8	57.3±13.0	56.5±10.8	0.70
History of smoking	26 (18.2%)	14 (20.3%)	12 (16.2%)	0.67
Body mass index	21.7±3.9	21.6±4.0	21.8±3.8	0.76
mMRC score	2.4±0.9	2.5±0.8	2.3±1.0	0.36
CAT score	26.0±6.4	26.9±5.9	25.2±6.8	0.13
Sputum weight, g/24 h	35.1±34.2	34.5±30.7	35.6±37.4	0.87
Sputum properties score	1.9±0.6	1.9±0.1	1.9±0.7	0.87
Disease etiology				
Postinfectious	93 (65.0%)	46 (66.7%)	47 (65.0%)	0.73
Idiopathic	50 (35.0%)	23 (33.3%)	27 (36.5%)	
Classification of lung CT				
Cylindrical bronchiectasis	62 (43.4%)	30 (43.5%)	32 (43.2%)	0.99
Varicoid bronchiectasis	14 (9.8%)	7 (10.1%)	7 (9.5%)	
Cystiform bronchiectasis	67 (46.9%)	32 (46.4%)	35 (47.3%)	
Pulmonary function				
FEV ₁ /FVC ratio, %	63.2±15.3	61.4±15.2	64.8±15.3	0.19
FEV ₁ , % predicted	55.8±22.8	54.7±22.3	59.7±22.1	0.14
FEV ₁ , L	1.4±0.6	1.3±0.6	1.5±0.6	0.07
Inflammation index				
Erythrocyte sedimentation rate	35.8±25.5	32.2±24.8	38.7±25.8	0.16
C-reactive protein	23.6±25.9	22.3±27.6	25.0±24.1	0.53

Data are expressed as *n* (%) or mean ± standard deviation. CAT, COPD Assessment Test; CT, computed tomography; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council.

Table 2. Comparison of drug usage of the study patients in the two groups

	Total	Intervention group	Control group	p value
<i>Local administration</i>				
Beta-2 receptor agonist nebulization	81 (54.4%)	40 (51.9%)	41 (56.9%)	0.541
M2 receptor blocker nebulization	50 (33.6%)	26 (33.8%)	24 (33.3%)	0.955
<i>Systemic administration</i>				
Theophylline drugs	94 (63.1%)	49 (63.6%)	45 (62.5%)	0.886
Ambroxol	92 (61.7%)	45 (58.4%)	47 (65.3%)	0.391
Meropenem	80 (53.7%)	38 (49.4%)	42 (58.3%)	0.272
Cefoperazone sodium or sulbactam sodium	54 (36.2%)	29 (37.7%)	25 (34.7%)	0.709
Ciprofloxacin or levofloxacin	87 (58.4%)	42 (54.5%)	45 (62.5%)	0.325
Piperacillin or tazobactam	32 (21.5%)	17 (22.1%)	15 (20.8%)	0.853
Length of antibiotic therapy, days	10.9±3.4	10.9±3.3	11.0±3.5	0.734

Data are expressed as *n* (%) or mean ± standard deviation.

Table 3. Comparison of sputum culture results between the two groups of patients before and after therapy

	Control group (n = 69)	Intervention group (n = 74)	χ^2 value	p value
Eradicated	16 (23.2%)	38 (51.4%)	14.211	0.03
Persistence	36 (52.2%)	19 (25.7%)		
Replacement	13 (18.8%)	12 (16.2%)		
Reinfection	4 (5.8%)	5 (3.5%)		

Data are expressed as n (%) unless indicated otherwise. Data include only subjects with cultures growing *P. aeruginosa* at baseline.

Table 4. Comparison of clinical indexes and lung function between the two groups before and after therapy

	Intervention group		Control group	
	before	after	before	after
<i>Clinical indexes</i>				
mMRC score	2.5±0.8	1.6±1.0	2.3±1.0	1.4±0.9
CAT score	26.9±5.9	22.2±7.2	25.2±6.8	19.6±7.6
Sputum weight, g/24 h	34.5±30.7	18.4±20.2	35.6±37.4	16.5±20.8
Sputum score	1.9±0.6	1.3±0.6	1.9±0.7	1.3±0.6
<i>Lung function</i>				
FEV ₁ /FVC ratio, %	61.5±15.2	62.2±13.8	64.8±15.3	64.7±15.7
FEV ₁ , % predicted	54.7±22.4	56.9±23.9	59.7±22.1	60.0±25.3
FEV ₁ , L	1.3±0.6	1.3±0.7	1.5±0.6	1.5±0.7

Data are expressed as mean ± standard deviation. CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council.

Discussion

Although nebulization of aminoglycosides has been used previously, to the best of our knowledge studies on amikacin nebulization for the treatment of BE exacerbation have not been published. Bilton et al. [15] showed that adding inhaled tobramycin to oral ciprofloxacin for 2 weeks showed no significant curative effects in patients with BE exacerbation at days 14 and 21. Pulmonary CF patients infected with *P. aeruginosa* experienced benefit from nebulization of amikacin liposomes in a phase II clinical trial. However, it is still a long road to achieving clinical application [16]. Our study showed that amikacin was suitable for nebulization therapy due to its taste, pH value, and osmotic pressure. The sputum weight, sputum property score, CAT score, and dyspnea score of the intervention group showed no significant difference compared to those of the control group. In a research report-

ed by Murray et al. [17], nebulization of gentamycin for 12 months did not improve pulmonary function. In our study, all indexes of the pulmonary function test significantly improved after therapy in both the control and the intervention group, but there was no significant difference between the two groups for FEV₁, FEV₁ (% predicted), or FEV₁/FVC ratio.

One study suggested that nebulization of antibiotics could eliminate *P. aeruginosa* [18]. In that study, nebulization of tobramycin (300 mg) twice daily for 4 weeks significantly decreased the bacterial density of *P. aeruginosa* after 2 weeks, without a further decrease 4 weeks later. The bacterial eradication rate of *P. aeruginosa* was 35% (13/37), with 3 patients developing drug resistance (according to fold point of drug resistance >16 mg/L) in the intervention group and 1 in the control group. Especially, patients in whom *P. aeruginosa* was eradicated after tobramycin solution for inhalation (TSI) therapy were

more likely to be assessed as clinically improved; 12 of 13 of the TSI patients (92%) with eradicated *P. aeruginosa* were assessed as improved, while only 11 of the remaining 24 TSI patients (46%) were assessed as improved. Bilton et al. [15] found that along with oral ciprofloxacin, nebulization of tobramycin for 2 weeks was not significantly different compared to the control group (34.6%, 18.5%), but the bacterial count of the sputum was significantly decreased. In our study, the bacteria eradication rate of the intervention group significantly increased up to 51.4%. The limitation of our study was failure to collect sputum further than the follow-up indicator; the bacterial eradication in the future is unknown.

Brodt et al. [19] collected 1,264 stable BE patients from 12 studies; compared to the control groups, the main advantages of inhaled antibiotics (such as amikacin, aztreonam, ciprofloxacin, gentamycin, colistin, or tobramycin) for 4–12 weeks were a decrease in sputum bacteria content, an increase in sputum bacterial eradication rate, and a decrease in the risk of BE exacerbation. The main adverse effect was bronchospasm, with approximately 10% morbidity. Another study by Yang et al. [20] screened 539 BE patients from eight randomized controlled trials and suggested that long-term treatment with nebulized antibiotics significantly decreased sputum bacterial density, increased the bacterial eradication rate of *P. aeruginosa*, and reduced the frequency of BE exacerbation. No evidence has suggested that nebulization therapy could increase *P. aeruginosa* drug resistance. The main adverse effect is bronchospasm or stridor.

Development of bacterial drug resistance is the most concerning adverse effect. Following nebulization of tobramycin for 24 weeks in CF patients, there was a concomitant trend toward an increase in the minimum inhibitory concentration (from 6.6 µg/mL at baseline to 18.2 µg/mL at the end of week 20) of isolated *P. aeruginosa* strains [11]. However, in the study reported by Drobnic et al. [21], compared to the control group, bacterial drug resistance did not change, with decreasing sputum bacterial content following nebulization of tobramycin (300 mg) twice daily for 6 months. Couch [18] found that 3 out of 36 patients with nebulization of tobramycin for 4 weeks and 1 out of 34 in the control group developed drug resistance. A study using a mouse model of nontuberculous mycobacteria lung infection showed that compared to a high dose of intravenous therapy, nebulization of amikacin liposomes had a similar curative effect, without increasing drug resistance [22]. The results described above illustrate that the nebulization of antibiotics does not increase drug resistance compared to intravenous therapy.

Nebulization of antibiotics is accompanied by local adverse effects, such as bronchospasm, cough, hoarseness, dysphagia, and dysgeusia. Patients who experienced bucking were not excluded in the study reported by Murray et al. [17], which led to numerous adverse effects: 21.9% of patients (7/32) in the intervention group experienced bronchospasm, whereas only 6% of patients (2/33) in the control group did so. No renal toxicity or ototoxicity occurred. Bilton et al. [15] found that 50% of patients suffering BE exacerbation had stridor. The morbidity was significantly higher compared to that of the control group. This result suggested large stimulation in airway and high morbidity of tobramycin nebulization. Only one bronchospasm event occurred in a study that screened 28 patients receiving nebulized amikacin liposome therapy [23]. Clancy et al. [16] verified no differences in the morbidity of adverse effects between nebulization of varying amikacin doses (70, 140, 280, and 560 mg) and control groups in a study that collected 105 samples from CF patients infected with *P. aeruginosa*. In our study, only 2 patients experienced bronchospasm due to nebulized amikacin (0.2 g), and renal toxicity or ototoxicity were absent. This may be related to the solution's properties and low dose of amikacin. With reduced local adverse effects of nebulized amikacin, patient compliance increases.

Ehrmann et al. [24] collected data from 6 healthy volunteers who received nebulized amikacin (40 mg/kg, 50 mg/kg, or 60 mg/kg) and found that it could be absorbed into the bloodstream, with corresponding concentration peaks in the plasma of 8.2 mg/L, 9.2 mg/L, and 9.2 mg/L, respectively. However, the plasma concentration of the highest dose of nebulized amikacin (9.2 mg/L, 60 mg/kg) was much lower than that of intravenous injection of amikacin (48 mg/L, 15 mg/kg). This result indicated that high-dose nebulized amikacin has little adverse effect on the general system. Luyt et al. [23] screened 28 patients supported by mechanical ventilation who were infected with gram-negative bacteria. The drug concentration in the alveolar epithelial lining fluid was 976.1 µg/mL following treatment with nebulized amikacin liposomes (400 mg) twice daily, and the drug plasma concentration was only 0.9 µg/mL, suggesting that very little amikacin was absorbed in blood following therapy. The high drug concentration in alveolar epithelial lining fluid was much greater than the minimum inhibitory concentration of amikacin.

In conclusion, nebulized amikacin therapy can be effectively applied in patients with exacerbation of BE. Having advantages regarding stability, low price, minor stim-

ulation in the airway, and effectiveness against *P. aeruginosa* with a high bacterial eradication rate, amikacin is suitable for BE patients in developing countries.

Statement of Ethics

The study protocol was approved by the Ethics Committee of Qilu Hospital, Shandong University (clinical trial registration No. NCT02081963). All patients gave written informed consent for participation in this study.

Financial Disclosure and Conflicts of Interest

There are no financial conflicts of interest for any authors regarding this work.

Author Contributions

Dr. Y. Li conceived and designed the study. C. Li and X. Wang collected the data. Y. Zhang and Q. Qi analyzed the data. T. Li helped draft the manuscript. All of the authors read and approved the final manuscript.

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