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Severe nosocomial pneumonia – emphasis on nebulized tobramycin

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ABSTRACT

Objective: To estimate the efficacy and safety of nebulized tobramycin (NT) as an adjunct to systemic antibiotics in the treatment of severe nosocomial pneumonia (NP). **Methods:** 25 mechanically ventilated patients (out of 150 screened) were enrolled in the current observational single-center study. They were randomized to receive either NT (300 mg, BID; group 1, $n=15$) as an adjunct to systemic antibiotics or for a correction of the regimen of systemic antibiotics (group 2, $n=10$). The primary outcome measure was resolution of NP and acute respiratory insufficiency. The CPIS, signs of systemic inflammatory response syndrome (SIRS) and oxygenation index were used as objective indicators of the clinical progress. **Results:** The following signs of NT efficacy were detected in 87% of group 1 patients: a decrease of SIRS and CPIS scores within (2.3 ± 1.2) d of NT therapy ($P<0.05$); decrease of microbes titer to 10^3-10^4 CFU/mL ($P<0.05$); increase of microbes sensitivity to systemic antibiotics in 40% of patients; positive X-ray dynamics in 60% of patients within (9.0 ± 2.5) d of NT therapy. No serious side effects of NT were observed. **Conclusions:** Administration of NT as an adjunct to systemic antibiotics is efficient and safe in 87% of patients with severe NP caused by multiresistant gram-negative bacteria.

1. Introduction

Nosocomial pneumonia (NP) remains one of the significant problems of the intensive care units worldwide. Associations of multiresistant gram-negative and gram-positive bacteria are prevalent agents of NP. Rational antibiotic therapy is the cornerstone of the treatment of NP. An early onset of antibiotic therapy improves the prognosis dramatically, but still the mortality and bacterial resistance are high. *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter* spp., *Burkholderia* spp., *Stenotrophomonas* spp. present with a property to form biolayers which protect them against antibiotics and immune cells[1–4].

Traditionally administered intravenous antibiotics do not reach a bactericidal concentration in the tissue of lungs: intravenously administered antibiotics are primarily detected in respiratory segments of lungs, but not in sputum. Increase of daily dosage and combining different antibiotics poses patients to a risk of multiresistance formation, side

effects and superinfection[3,5–8].

Inhaled colistin, tobramycin, cephalosporins, amphotericin B, pentamidin have been used for prophylaxis and treatment of chronic and acute pseudomonal infections in patients with cystic fibrosis and bronchiectases for more than 50 years[9–14]. A 28 d course of the nebulized tobramycin (NT) was proved to be effective in eradication of *P. aeruginosa* in patients with cystic fibrosis[15].

Many research papers proved that nebulized antibiotics as adjuncts to systemic drugs decrease the degree of pulmonary inflammation, facilitate weaning patients from ventilation, decrease microbial titer in bronchoalveolar lavage fluid (BAL)[16–19]. Lu Q *et al* showed a comparable clinical efficacy of systemic and nebulized cephalosporins and amikacin, but less frequent formation of multiresistant strains of *P. aeruginosa* in the group of nebulized antibiotics[20]. Inhaled fluoroquinolones[21], liposomal aminoglycosides[22], aztreonam[23], combinations of nebulized antibiotics (phosphomycin/tobramycin[24–25], colistin/tobramycin[26], ciprofloxacin/colistin[27]) are of good future. Effect on biofilms is one of the significant mechanisms of the action of nebulized antimicrobials[28].

Inhaled antibiotics are not administered without systemic drugs because the degree of their adsorption is low (2%–4%)

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and insufficient for the treatment of infections associated with NP which is common in intensive care unit patients. The incidence of the side effects of nebulized antibiotics is low. One of the pitfalls of modern nebulized aminoglycosides is the small size of particles which speeds up their clearance from lungs[9,29–33].

Only few clinical trials and case reports on NT in nosocomial pneumonia in critically ill patients were carried out[16,33–34]. The objective of the current investigation was to estimate the efficacy of NT as an adjunct to systemic antibiotics in the treatment of severe NP in critically ill patients.

2. Materials and methods

Twenty five mechanically ventilated patients out of a cohort of 150 surgical intensive care unit patients were enrolled in the current observational single-center study within the period of 2009–2012 at the V.A. Negovsky scientific research institute of general reanimatology of the Russian academy of medical sciences (Moscow, Russia). The current investigation received the formal approval from the local Ethical Committee and written informed consents were obtained from all the enrolled subjects or their legal representatives. The research was conducted in accordance with the Declaration of Helsinki, national and institutional standards.

Inclusion criteria: age 18–65 y.o.; mechanically ventilated intensive care unit patient; positive NP criteria; failure of the current antibiotic regimen (absence of positive clinical dynamics of NP, progression of acute respiratory insufficiency and SIRS).

Exclusion criteria: APACHE II >26; acute kidney insufficiency, requiring hemodialysis; severe concomitant sub- or decompensated diseases of kidneys, liver, heart, vessels, diabetes mellitus; immune deficiency; hearing or vestibular disorders.

All patients were males, aged (49.0±7.3) y.o. No reliable differences in severity were detected between the groups prior the randomization: APACHE II on the day of enrollment was (18.0±3.2) in group 1 and (17.7±3.5) in group 2; Clinical Pulmonary Infection Score (CPIS) was (8.5±2.4) in group 1 and (8.2±2.0) in group 2.

Twenty five patients were randomized (using envelopes) in two groups: group 1 (interventional) and group 2 (control). Group 1 received NT (group 1, $n=15$) as an adjunct to systemic antibiotics; the basic antibiotic regimen remained unchanged. Group 2 experienced a correction of the regimen of systemic antibiotics (group 2, $n=10$) according to bacterial sensitivity to iv tigecycline ($n=3$, 30%); iv amikacin 1.0–1.5 g/d was added to therapy ($n=4$, 40%); daily dosage of iv meropenem was increased up to 6 g ($n=3$, 30%).

The primary outcome measure was resolution of NP and acute respiratory insufficiency. The CPIS, signs of SIRS and

oxygenation index were used as objective indicators of the clinical progress.

Nosocomial pneumonias were ventilator-associated in 100% of patients. NP developed in patients with severe intraabdominal infections (group 1 $n=8$, 54%; group 2 $n=6$, 60%), purulent mediastinitis (group 1 $n=4$, 27%; group 2 $n=3$, 30%), intracerebral abscesses (group 1 $n=2$, 14%; group 2 $n=1$, 10%), tracheoesophageal fistulas (group 1 $n=1$, 5%; group 2 $n=0$). Nosocomial pneumonia was diagnosed on the transmission patients to our intensive care unit (ICU) from other hospitals in 6 patients and developed within (5.3±0.9) d from the admission to our ICU in 14 patients. Nosocomial pneumonia was diagnosed according to the Russian national guidelines[35] and CPIS[36]. Pneumonias were bilateral and polysegmental in 100% of patients (confirmed by the X-rays (performed on enrollment, on days 5, 7, 14) and computed tomography scans). The acute respiratory distress syndrome (ARDS) on the background of NP was diagnosed according to the criteria of the V.A. Negovsky scientific research institute of general reanimatology[37–39] in 4 patients of group 1 (27%) and in 3 patients of group 2 (30%). Sepsis was diagnosed in 100% of patients on enrollment using the standard criteria[40]. All patients experienced a withdrawal of the biological samples for the microbiological essay (analyzer “VNTEK Compact”, Biomerieux, France) on enrollment, on days 5 and 7. BAL samples were taken during the bronchoscopy in the operation room or in the ICU. Transport media “MEUS S.r.l.” (Pieve di Sacco, Italy) was used. Preliminary results of the microbiological study were available within 12 h, the detailed result – within 3–4 d.

Associations of 2–4 multiresistant gram-negative microbes 10^7 – 10^8 CFU/mL were detected in all patients. Associations of gram-negative and gram-positive microbes were detected in 3 patients. No reliable differences in the incidence of microbes were detected (Table 1).

At the moment of NT administration (group 1) or the correction of the antibiotic regimen (group 2) patients of both groups were treated with meropenem (1 g TID – $n=20$, 80%), imipenem/cilastatin (500 mg 4 times/d – $n=3$, 12%), piperacillin/tazobactam (4,5 g TID – $n=2$, 8%); 3 patients (12%) were additionally treated with linezolid (600 mg BID) for Staphylococcus aureus infection; 3 patients (12%) – voriconazole 200 mg/d for invasive Candida albicans infection. None of the patients received systemic aminoglycosides.

Nebulized tobramycin was administered in group 1 in case of inefficacy of the systemic antibiotics (no positive clinical dynamics and deterioration of the acute respiratory insufficiency and SIRS due to NP), simultaneously with systemic antibiotics on day (6.5±1.4) of the treatment of NP, 300 mg BID. The daily dosage of NT was reduced to 300 mg/d in case of creatinine clearance less than 50 mL/min ($n=2$, 20%). Tobramycin was nebulized by “Aeroneb Pro” (Aeroneb, Ireland) nebulizer. The duration of NT therapy was (7.5±2.4) d. The following criteria were used for the discontinuation

of NT: positive clinical dynamics (decrease of SIRS and acute respiratory insufficiency signs). Systemic antibiotics were normally continued in group 1 for the treatment of the background infections.

Patients of both groups were treated for sepsis and ARDS using the international and institutional standards. Mechanical ventilation was performed by means of Puritan Bennett 840 (Puritan–Bennett Corporation, USA). Synchronized intermittent mandatory ventilation and BiLevel, volume- or pressure-controlled ventilation modes were used.

Adverse events reporting, audiometry, and renal function were monitored to evaluate the tolerability and safety of the NT regimen. No patients were withdrawn from the study for adverse events.

Data were statistically analyzed by means of Statistica 7.0 pack. Mean (M), standard deviation (σ), *Newman–Keuls* test, *Mann–Whitney* test were calculated. $P < 0.05$ was considered statistically significant.

3. Results

Table 2 deals with the dynamics of the key physiological parameters in groups 1 and 2. No statistically reliable differences (intergroup or between days) were obtained within 8 d of investigation, which can probably be explained by the small sample size and influences of the background

infectious complications (peritonitis, mediastinitis, etc.)

Administration of NT in group 1 was clinically effective and decreased the signs of SIRS (decrease of body temperature, leukocytosis and amount of purulent discharge from the airways) and acute respiratory insufficiency (increase of the oxygenation index, decrease of the CPIS scores) within 2.3 ± 1.1 d from the treatment start in 13 patients in group 1 (87%). The decrease of SIRS signs in group 2 in comparison to group 1 was detected reliably later – 6.3 ± 1.5 d after the shift of antibiotics ($P < 0.05$).

A reliable decrease ($P < 0.05$) of the titer of pathogenic microbes in BAL on days 5 and 7 in comparison of the titer on enrollment was detected: down to 10^3 – 10^4 KFU/mL in group 1 (87% of patients) and in group 2 (50% of patients). Microbes in BAL of 13 patients of group 1 were in vitro sensitive to tobramycin; 2 patients of group 1 (13,4%) presented with in vitro resistance to tobramycin, but still the clinical efficacy of NT was shown in them – probably due to a high local concentration of the nebulized antibiotic [9,32]. An increase of the sensitivity of microbes to antibiotics they were resistant to, prior the NT therapy, was detected in group 1 (40%), which is probably due to the action of NT on biofilms [26].

Positive X-ray and chest computed tomography dynamics was detected in 6 patients (40%) of group 1 within 9.0 ± 2.5 d (Figure 1); there were no such dynamics in group 2. Three patients of group 1 were switched to the continuous positive airway pressure ventilation with pressure support on day 5.2

Table 1

Results of the microbiological studies of BAL.

Group 1 (n=15) (nebulized tobramycin)		Group 2 (n=10) (intravenous antibiotics)	
Microbes	Patients n(%)	Microbes	Patients n(%)
<i>Pseudomonas aeruginosa</i>	12 (80%)	<i>Pseudomonas aeruginosa</i>	7 (70%)
<i>Acinetobacter baumannii/calcoaceticus</i>	9 (60%)	<i>Acinetobacter baumannii/calcoaceticus</i>	6 (60%)
<i>Klebsiella pneumonia</i>	3 (20%)	<i>Klebsiella pneumonia</i>	3 (30%)
<i>Proteus mirabilis</i>	3 (20%)	<i>Proteus mirabilis</i>	2 (10%)
<i>Staphylococcus aureus</i> MRSA	1 (7%)	<i>Staphylococcus aureus</i> MRSA	1 (10%)
<i>Enterococcus faecalis</i>	1 (7%)		

Table 2

Dynamics of body temperature, leukocytosis, heart rate, mean blood pressure, oxygenation index in groups 1 and 2 within 5 d of investigation (M \pm σ).

Group	Day	Temperature(°C)	Leukocytosis(103/mcl)	Heart rate(1/MNH)	Mean blood pressure(mmHg)	Oxygenation index(mmHg)
1	–1 day	38.0 \pm 0.7	14.9 \pm 9.7	101.2 \pm 12.1	58.9 \pm 13.2	173.8 \pm 36.8
	Day 1	38.1 \pm 0.5	20.0 \pm 14.0	100.3 \pm 13.2	61.5 \pm 11.0	195.0 \pm 60.1
	Day 2	37.9 \pm 0.7	13.6 \pm 8.7	98.5 \pm 10.3	63.4 \pm 13.7	192.6 \pm 54.8
	Day 3	37.6 \pm 0.5	14.3 \pm 8.8	99.2 \pm 10.5	59.3 \pm 8.0	206.1 \pm 44.6
	Day 4	37.6 \pm 0.7	11.8 \pm 7.8	92.6 \pm 13.2	60.5 \pm 6.5	198.2 \pm 38.9
2	Day 5	37.4 \pm 0.8	13.6 \pm 10.3	94.5 \pm 10.6	68.2 \pm 11.1	200.8 \pm 38.5
	–1 day	37.8 \pm 0.7	11.2 \pm 3.9	105.7 \pm 11.1	57.5 \pm 22.0	211.0 \pm 61.4
	Day 1	38.1 \pm 0.6	13.0 \pm 5.0	99.6 \pm 12.3	63.6 \pm 6.5	219.0 \pm 65.8
	Day 2	37.7 \pm 0.7	14.3 \pm 5.4	97.5 \pm 11.0	66.7 \pm 7.1	211.7 \pm 56.6
	Day 3	37.5 \pm 0.6	14.2 \pm 3.5	90.2 \pm 9.6	63.7 \pm 9.6	216.6 \pm 60.7
	Day 4	37.3 \pm 0.6	16.5 \pm 8.1	94.2 \pm 10.2	61.2 \pm 6.9	218.8 \pm 60.5
	Day 5	37.5 \pm 0.7	12.4 \pm 2.5	90.5 \pm 11.6	63.1 \pm 5.1	216.3 \pm 65.8

Note: –1 day: the day before the enrollment.

±1.7 of NT treatment.

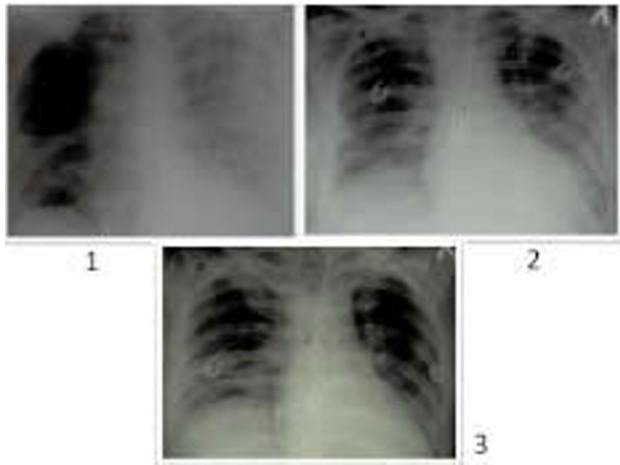


Figure 1. Positive X-ray dynamics in a patient treated with NT (1: before the treatment; 2: day 5 of treatment; 3: 14 d after the onset of treatment).

In 2 patients of group 1 (13.4%, underlying pathology – intraabdominal infections) NT was ineffective and the antibiotic regimen was switched to iv tigecycline in standard doses, which finally provided us with a favourable outcome of NP. The failure of NT regimen was probably due to multi-resistant strains of *P. aeruginosa* and *Acinetobacter baumannii/calcoaceticus* detected in these patients.

The mortality in group 1 was 27% ($n=4$), in group 2 – 30% ($n=3$). None of the deaths were associated with the progression of NP. Partial hearing loss and tinnitus were registered in 2 patients (14%) of group 1 after the administration of NT. These symptoms resolved spontaneously 3 months after the discontinuation of NT. It is noteworthy that these patients had a very prolonged period of ICU stay (100–120 d) due to the severity of the background infections, therefore the influence of sepsis and other treatment modalities on the development of hearing loss and tinnitus cannot be excluded. There were no cases of bronchospasm or kidney damage registered, which corresponds well with the data of the other investigations^[9,29–33].

We are under way of constructing a multi-center trial in a bigger population of ICU patients, with a simultaneous analysis of NT pharmacokinetics.

4. Discussion

Administration of the nebulized tobramycin 300 mg BID as an adjunct to systemic antibiotics is efficient and safe in 87% of patients in treatment of severe nosocomial pneumonia caused by multiresistant gram-negative bacteria.

Conflict of interest statement

We declare that we have no conflict of interest.

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