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Comparative Study between Combined Intravenous and Nebulized Amikacin versus Intravenous Amikacin Alone for Treatment of Ventilator Associated Pneumonia

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ABSTRACT

Background: Ventilator-associated pneumonia [VAP] is a type of infection affecting the lower part of the respiratory system related to the intubation of trachea.

Patients and methods: An observational randomized prospective study approved by the ethical committee of Mustasharak Hospital, Saudi Arabia, and was conducted in the period from June 2021 to May 2022. Patients were randomly categorized into two primary groups using a randomized and computer-generated table. The first group [group NI; n=31] received intravenous and nebulized amikacin, while the second group [group [I]; n=31] and only received intravenous amikacin.

Result: Pseudomonas infection accounted for about 65% of patients in group NI, and 40% in group I. Klebsiella infection was 30% in group NI, and 25% in group I. Acinetobacter infection was approximately 15% in group NI and 40% in group I. The Clinical Pulmonary Infection [CPI] score for group NI was ≤ 6 in 73% of patients. In group I, the CPI score was ≤ 6 in 54%. Oxygenation within Group NI significantly improved before, and after treatment [p 0.005]. However, in group I, no change was discovered [p 0.209]. Creatinine level was significantly high in group I after treatment.

Conclusion: Nebulized amikacin is considered a safe and effective treatment option for VAP.

Keywords: Ventilator; Pneumonia; Infection; Amikacin.

INTRODUCTION

Ventilator-associated pneumonia is a type of lung infection that occurs in patients on a mechanical ventilator. It often leads to substantial mortality and morbidity among critically ill patients [1]. VAP is among the most prevalent diseases in the ICU. Approximately 10% of all mechanically-ventilated patients have higher chances of developing VAP [2]. According to Cook *et al.* [3], the risk of VAP increases with the increased duration of mechanical ventilation and reaches its peak point on day five following intubation. VAP is further related to a high morbidity rate as it lengthens the ICU stay period, the duration of mechanical ventilation, as well as the hospital stay period [4].

VAP is usually a result of multiple drug-resistant organisms [MDROs] and its association with the high fatality rate. [5] Some examples of potential MDROs are Klebsiella, Acinetobacter spp., which leads to carbapenemase, Stenotrophomonas malto-philia, ESBL, which causes Enterobacteria-ceae, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus [5].

The diagnosis of VAP requires a mingled evaluation of clinical data, radiological findings, and microbiological results [6]. There is no easy and simple tool available for VAP diagnosis. In cases when VAP is highly questionable, there is always an immediate administration of empirical anti-microbials since both inadequate treatment and delayed management lead to an increased incidence of mortality and morbidity [6].

Gram-negative bacilli should be empirically covered with a third or fourth-generation cephalosporin, piperacillin-tazobactam, carbapenem, combining them with a fluoroquinolone or an aminoglycoside [7]. The increase in inadequate infection treatment incidences is among the sequelae of antimicrobials resistance increased prevalence [8]. However, there are alternatives for Gram-negative MDR bacilli treatment. Administering inhaled antibiotics delivers high drug levels in both lungs and reduces the systemic toxicity associated with intravenous antimicrobials [8]. High concentrations of inhaled antibiotics within the respiratory systems may increase in folds ranging from 20 to 100 compared to MIC of the treated pathogens [8].

AIM OF THE WORK

An increased antimicrobials resistance, especially due to inadequacy of new antimicrobials development, increases the need for novel treatment strategies to optimize the already existing microbial pharmacodynamics [7]. This will help preserve the efficacy of antibiotics, reduce resistance emergence, and give pharmaco-economic benefits.

PATIENTS AND METHODS

This is an observational randomized prospective study. The study was approved by the ethical committee of Mustasharak Hospital, Saudi Arabia, and was conducted within the period from June 2021 to May 2022. After obtaining informed consent acquired from the legal attenders of patients, the study was conducted on 62 males as well as a female patient who had been infected with VAP. Patients were randomly categorized into two primary groups using a randomized and computer-generated table. The first group [NI group] with n= 31 received intravenous and nebulized amikacin, while the second group [I group] with n=31 only received intravenous amikacin.

This study comprised patients above the age of 18 years and had been admitted to the ICU. Any type of pneumonia between 48 and 72 hours or thereafter due to mechanical ventilation is diagnosed as VAP. It is characterized by progressive or new lung infiltrates, detection of the causative agent, sputum characteristics change, and signs of systemic inflammatory disease, including a change in white blood cell count as well as fever [4].

Exclusion criteria for the study: In the present study, exclusion criteria included patients who could not get their guardians' consent to take part in the research, cases with allergies or developed resistance to amikacin, and patients with creatinine clearance below 60 mL/h or PaO2/PiO2 less or equal to 100 mmHg. The study also excluded cases where patients experienced an increased Clinical Pulmonary Infection Score [CPIS] [9] [Table 1], or patients with positive cultures even after eight days and later moved to intravenous amikacin of about 20mg/kg/day.

Table [1]: Parameters of the CPIS score [9]

Body temperature	• ≥ 36.5 or ≤ 38.4 • ≥ 38.5 or ≤ 38.9 • ≥ 39 or < 36.5	0 point 1 point 2 points
Total leucocytic count	• ≥ 4000 or ≤ 11.000 • <4000or>11.000 • Rod form ≥ 50%	0 point 1 point add 1point
Tracheal secretion	• Tracheal secretion [−] • Tracheal secretion with less purulence • Abundant purulent secretion	0 point 1 point 2 points
Oxygenation	• Pa02/Fi02, mmHg >240 or ARDS [ARDS: Pa02/Fi02 < 200, Pa02/Fi02 < 200, PAWP ≤ 18 mmHg and bilateral acute infiltration] • Pa02/Fi02, mmHg ≤ 240 or ARDS	0 point 2 points
Pulmonary infiltration in chest X-ray	• No infiltration • Diffuse infiltration • Localized infiltration	0 point 1 point 1 point
Progression in pulmonary infiltration	• Radiographic progression [−] • Radiographic progression [+] [after the exclusion of HF and ARDS]	0 point 2 points
Pathogenic bacteria in tracheal aspirate culture	• No or few pathogenic bacteria • Moderate or high levels of pathogenic bacteria • Pathogenic bacteria to be seen in Gram staining	0 points 1 point add 1 point

Procedures of the Study: Either nebulized and intravenous amikacin or only intravenous amikacin on a random basis were given to patients after meeting the eligibility criteria in both groups. In group [NI], nebulization of amikacin 15 mg/kg in 10 mL was performed every day in a daily dose alongside another intra-venous amikacin dose of 15 mg/kg/day. In the second group [I], the daily dose included normal saline nebulization of 10mL with 20 mg/kg/day of intravenous amikacin. The two groups were given standard ICU treatment protocol of antipyretics, anti DVT, and anti-PUD prophylaxis. CPIS daily assessment and the monitoring of laboratory and clinical parameters were applied and recorded. Patients who had increasing CPIS and positive cultures led to the end-of-study authorization after eight days and also resulted in shifting to intravenous amikacin of about 20 mg/kg/day. Nebulization was carried out using vibrating plate nebulizers that had specific ventilation settings.

Statistical analysis

The gathered data were re-examined, tabulated, coded, and analyzed using the SPSS software [SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001]. Both mean and standard deviation [± SD] were used to present the quantitative parametric data. Quantitative non-parametric data were presented using both the interquartile range and median. Percentage and frequency were used to present qualitative data. The data obtained determined the most appropriate analysis for the study. Quantitative data were analyzed using T-test or Mann-Whitney test. On the other hand, qualitative data were analyzed using Fisher extract test and chi-square test. The study considered a p-value of <0.05 as statistically significant.

RESULTS

During this study, 81 patients were screened. The study excluded 11 patients who did not meet inclusion criteria, while the legal guardians of 8 patients rejected to take part in the research. Only 62 patients were left and randomly allocated to the research's various groups.

Patient Data: Patients in both groups did not show any significant differences in sex, age, and ICU admission causes, as presented in Table [2].

Causative Agents: Pseudomonas infection accounted for about 65% in group NI, and 40% in group I. Klebsiella infection was 30% in group NI, and 25% in group I. Acinetobacter infection was 15% in group NI and 40% in group I. As shown in Table [3], the organisms did not reveal any significant differences from cultures.

CPI Score and Clinical Cure: The CPI score for group NI was ≤ 6 in 73%. In group I, the CPI score was ≤ 6 in 54%, and there were no significant differences, as shown in Table [4].

Treatment efficiency, adverse effects, and ICU stay length: Oxygenation within Group NI significantly improved before and after treatment [p 0.005]. However, in group I, no change was discovered [p 0.209]. This is illustrated in Table [5].

Group NI had a length of stay [LOS] of about 20.8 while group I had 24.6. A substantial decrease was discovered in the first group versus the second group [about p 0.039]. The MV duration in group NI was about 17, while in group I it was approximately 24. Ventilation days were significantly reduced [p 0.044] [Table 6].

Creatinine level was significantly high in group I after treatment [p < 0.002], but creatinine was not significantly high in group NI. At the end of treatment, there was a significant difference between groups NI and I [Table 7].

Microbiological response: Regarding organism clearance, it was 81.3% in group NI versus 23% in group I. Resistance was 6.1% for group NI versus 27.7% in group I. As for superinfection, it was 2.9 in group NI versus 20.8% in group I. Combined superinfection and resistance was 6.0 % in group NI versus 24.3% in group I. Finally, regarding the organism clearance after treatment, there was a significant variation between both [Table 8].

ICU Mortality: Group NI had 18 mortalities, which accounted for about 59%. Group I experienced a mortality of about 25 patients, which constitutes [79%]. Therefore, group I exhibited a higher mortality rate than group NI, however the difference was not statistically significant [Table 9].

Table [2]: Patients data and ICU causes of admission

		Total [N=62]	Group NI [N=31[	Group I [N=31[	NI/I
Age [years]	Mean ± SD	58.3 ± 17	57.0 ± 14.4	58.3 ± 17.4	0.681*
	Range	27.0–87.0	24.0–89.0	27.0–87.0	
Sex	Male	48 [76%]	20 [64.0%]	27 [86%]	0.277#
	Female	14 [24%]	11 [36.0%]	4 [14%]	
Comorbidities	DM	16 [26%]	7 [25.0%]	8 [28%]	0.721#
	HTN	19 [31%]	09 [30.0%]	09 [30%]	0.734#
Causes of admission	Respiratory	51 [80%]	29 [94.0%]	21 [68%]	0.149#
	surgical	25 [39%]	10 [34%]	14 [45%]	0.521#

*: independent t test; #: Chi-square test

Table [3]: Correlation between study groups in regard to organisms disclosed from cultures prior to treatment

	Group NI	Group I	NI/I
Klebsiella	10 [30.0%]	5 [25.0%]	0.278
Acinetobacter	5 [15.0%]	13 [40.0%]	0.047
Pseudomonas	20 [65.0%]	13 [40.0%]	0.121
Citrobacter	0 [0.0%]	1 [4.5%]	0.309
Staphylocci	0 [0.0%]	2 [9.0%]	0.151
Provedinetia	1 [4.5 %]	1 [4.5 %]	1.010
Proteus	1 [4.5 %]	1 [4.4%]	1.010
Enterobacter	1 [4.4%]	0 [0.0%]	0.308

Table [4]: Correlation between study groups in regard to the CPIS score following treatment

CPIS	Group NI	Group I	NI/I#
≤ 6	23 [73.0%]	17 [54.0%]	0.174
> 6	7[27.0%]	13 [46.0%]	

#Chi-square test

Table [5]: Correlation between groups as regards oxygenation [Pao2/Fio2]

		Group NI	Group I	NI/I^
Before	Median [IQR]	163.4 [145.3–231.1]	162.0 [151.0–191.7]	0.568
	Range	103.0–398.0	102.0–249.0	
After	Median [IQR]	187.0 [160.1–228.1]	171.3 [152.0–219.9]	0.270
	Range	140.0–400.0	119.0–279.0	
Difference	Median [IQR]	19.7 [− 6.1–40.9]	22.0 [− 9.0–50.1]	0.793
	Range	− 29.0–59.0	− 101.0–149.0	
	***p*#**	**0.005***	0.210	

Negative values demonstrate reduction; IQR interquartile range; ^Mann-Whitney test; #Wilcoxon signed rank test

Table [6]: Correlation between groups in regard to the period of mechanical ventilation and length of stay in days

		Group NI	Group I	NI/I^
Duration MV	Median [IQR]	17.0 [15.1–25.4]	24.0 [22.1–25.0]	**0.035***
	Range	12.0–89.0	21.0–35.0	
Length of stay	Median [IQR]	20.8 [15.7–26.0]	24.6 [22.0–26.6]	**0.041***
	Range	14.0–87.0	21.0–36.0	

IQR: interquartile range

Table [7]: Comparison between case and control groups as regards creatinine [mg/dl]

Creatinine		Group NI	Group I	A/B^
Before	Median [IQR]	1.09 [0.80–1.28]	1.13 [0.83–1.27]	0.589
	Range	0.58–2.27	0.79–1.82	
After	Median [IQR]	1.00 [0.75–1.25]	1.29 [1.22–1.52]	**0.002***
	Range	0.21–2.01	0.81–2.48	
Difference	Median [IQR]	0.00 [-0.26–0.12]	0.12 [0.04–0.30]	**0.012***
	Range	-2.11–1.00	0.00–1.55	
	***p*#**	**0.449**	**< 0.001***	

Negative values indicate reduction; IQR: interquartile range; ^Mann-Whitney test; #Wilcoxon signed rank test; *Significant

Table [8]: Correlation between study groups in regard of organism clearance after treatment

	Group NI	Group I	x^2	*p* value
No growth	27 [81.3%]	8 [23.0%]	20.43	**< 0.001***
Resistance	2 [6.1%]	9 [27.7%]	4.952	**0.036***
Superinfection	1 [2.9%]	7 [20.8%]	3.571	**0048***
Resistance and superinfection	2 [6.0%]	8 [24.3%]	3.721	**0.045***

Chi-square test; *: significant

Table [9]: Correlation between study groups in regard of ICU mortality

Time	Group NI	Group I	NI/I#
Death	18 [59.0%]	25 [79.0%]	0.171

DISCUSSION

Nebulized administration of antibiotics provides a benefit of attaining high drug concentrations at the site of the infection with a low systemic absorption. As a result, the side effects of the drugs are reduced. Nebulized antibiotics are significantly beneficial in the systemic antibiotic treatment for minimizing morbidity, as well as mortality resulting from VAP. Intravenous antibiotics fail to reach a bactericidal concentration in every different lung tissue. Intravenously administered antibiotics are mainly recognized in the lung segments. They are not present in the sputum. Therefore, an increase in the daily dosage, as well as a combination of various IV antibiotics cause more adverse effects to patients [11].

The risk of developing VAP is elevated by endotracheal tube placement by about 6-20 folds in comparison with the critically-ill un-intubated patients. Niederman *et al.* [12] concluded that the attributable rate of mortality in VAP patients is about 47%, as compared to the 22% in the entire population of ICU patients.

The results of the current study indicated that the VAP therapy using nebulized amikacin results in reduced ventilation, as well as ICU stay, increased rates of oxygenation, increased clearance of bacteria with insignificant resistance as well as superinfection, and little nephrotoxicity if utilized as an adjunctive treatment to treat VAP resulting from MDR Gram-negative bacteria. The combined group [NI] was associated with less mortality related to VAP, as well as a higher score of CPIS.

The research conducted by Lu *et al.* [2] included 40 VAP patients who were engaged in a trial to compare nebulized ceftazidime and nebulized amikacin against the IV ceftazidime and amikacin. VAP resulted from *Pseudomonas aeruginosa*. In the study, twenty patients were given nebulized ceftazidime of 15 mg/kg/3 h as well as amikacin of

25 mg/kg/day against 17 patients who received intravenous ceftazidime of 90 mg/kg/day and amikacin of 15 mg/kg/day. The findings indicated that organism clearance was about 55% [p 0.33]. Resistance was recorded as 15% against 30% [p 026]. The researchers recorded a superinfection of about 15% against 15% in nebulized against IV groups given that the difference was statistically insignificant. An increased rate of clearance in the group that was nebulized in comparison with the IV group. However, the statistical insignificance might have resulted from the use of a smaller sample of forty patients, the use of another antibiotic [ceftazidime] with different pharmacodynamics as well as pharmacokinetics, the use of nebulized antibiotics for about eight days, and using the vibrating mesh nebulizer rather than the jet nebulizer in the study. Jet nebulizers can be used for delivering tiny particles of antibiotics deeper in the bronchial tree [2].

Lu *et al.* [13] examined 165 VAP patients. The VAP resulted from *A. baumannii* and *P. aeruginosa*. The stain group was very sensitive. It comprised of 122 VAP patients who were vulnerable to β-lactams, quinolones, and amino-glycosides. They were treated using intravenous antibiotics for two weeks. Fourty-three VAP patients became part of the multi-drug resistant group. The patients were given high dose of nebulized colistin as treatment in monotherapy or as a combination to the three-day intravenous aminoglycosides for about 7 to 19 days. It was discovered that the nebulized group had MV median duration of approximately 18 days while the control group exhibited MV duration of about 38 days [p 0.001]. According to Lu *et al.* [13], the difference in findings can be associated with the big sample size used, as well as the use of nebulization in combination with the IV routes, and the utilization of jet nebulizers.

Another study examined 90 VAP patients who were administered IV amikacin 20 mg/kg/day as well as meropenem 2g/8h to the first group. The second group was given nebulized amikacin 25 mg/kg/day. The third group was offered IV amikacin 20 mg/kg/day, nebulized amikacin of 25 mg/kg every day, as well as an extended meropenem 2g/kg/8h infusion for about 3 hours. The second group indicated a high statistically significant decrease in the days of the ventilator [about 5.31 ± 1.86 vs 7.3 ± 2.1 days [p < 0.001]]. The third group exhibited significantly fewer days of ventilation in comparison with the first group [4.22±1.32 vs 5.32 ± 1.86 [p < 0.011]] [14]. The similarity might have resulted from the huge sample used, the combination of nebulized and IV routes, and the utilization of jet nebulization [14].

The study conducted by Hassan *et al.* [15] involved 133 patients who were examined in post-cardiac surgery ICU. They administered inhaled amikacin at a 400 mg dose two times a day for a week to the group of the nebulizer. The IV group was given IV amikacin in a 20 mg/kg dose IV for one week. Both groups were also given IV piperacillin or tazobactam empirically as per the unit antibiogram. It was discovered that the values of creatinine clearance had a high significant decrease before, and after the end of the therapy between the two groups. The nebulized group had a reduction rate of about 10 ml/min [0-27]. The IV group, on the other hand, had a reduction rate of about 16 mL/min [8-30].

The study had comparable results, regarding mortality between the two groups, with no significant differences. These results are in line with the past studies conducted. Lu *et al.* [13] found that the nebulized group had a mortality rate of about 10% while the IV group had a mortality rate of 5%. There were no significant differences in the results. According to Ammar and Abdalla [14], the IV group had a VAP mortality rate of about 8% while the nebulized group, as well as the extended IV infusion group had a rate of approximately 4% [p 0.717]. The differences were insignificant.

Limitations: The study had no limitations.

Conclusion: Nebulized amikacin is considered as a safe and effective VAP treatment option. However, it is essential to conduct more studies to examine the safety and efficacy of nebulized antibiotics in VAP treatment, as well as the possibility to be used as prophylactic and empirical independent therapies to minimize the adverse effects and toxicity of the systemic antibiotics. This would help in ascertaining the significant superiority of the nebulization regimen to the IV-alone regimen of treatment of VAP.

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