Randomized Control Study of Nebulized Colistin as an Adjunctive Therapy in Ventilator-Associated Pneumonia in Pediatric Postoperative Cardiac Surgical Population

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) with multidrug-resistant (MDR) gram negative organisms is a common problem in intensive care unit (ICU). Aerosolized antibiotics enhance the efficacy of systemic antibiotics when added as adjuvants.

Aim: The primary objective of the study was to compare the clinical and bacteriological outcome of patients with VAP who were administered intravenous (IV) antibiotics alone with those patients who were treated with adjunctive nebulized colistin (NC) along with IV antibiotics. The secondary objective was to study the occurrence of any adverse events during colistin nebulization.

Settings and Design: The study was a prospective, randomized, double-blinded controlled study conducted at a tertiary-care teaching institution.

Materials and Methods: Ninety-eight children from surgical ICU aged less than 12 years who were diagnosed with VAP due to gram negative bacteria following cardiac surgery were chosen and divided randomly into two groups. The experimental group (NC group) was treated with systemic antibiotics along with NC, whereas the control group (NS group) was administered systemic antibiotics with nebulized normal saline (NS). Clinical and bacteriological outcomes were noted. Statistical analysis was done using SPSS Version 20.0 software. The patient characteristics were compared using independent Student’s t-test and Chi-square test.

Results: There was a statistically significant reduction in the duration of mechanical ventilation, postoperative ICU and hospital stay (P < 0.05) in the NC group compared with the NS group.

Conclusion: Aerosolized colistin may be considered as an adjunct to systemic IV antibiotics in pediatric patients with VAP due to gram negative bacteria susceptible to colistin.

Keywords: Colistin, gram negative bacteria, nebulized antibiotics, ventilator-associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the frequent nosocomial infection in the surgical intensive care unit (SICU), with an incidence ranging from 5% to 40%.[1] It is often associated with prolonged hospitalization, increased health care costs, and has an average of 10% attributable mortality.[1] There is an increasing occurrence of multidrug-resistant (MDR) gram negative bacterial infections with pathogens such as Pseudomonas aeruginosa,
extended-spectrum β-lactamase producing *Klebsiella pneumoniae* and *Acinetobacter baumannii* in intensive care unit (ICU) patients who develop VAP.\[^5,6\] It is often caused due to prolonged duration of endotracheal intubation. Studies have demonstrated that endotracheal intubation in pediatric patients beyond 30 days was associated with a 40% risk of VAP.\[^5,6\]

From early 2000, antimicrobial resistance (MDR) in gram negative bacteria has been a worrisome problem in ICU patients. As the possible antimicrobial options are limited, there is increasing use of intravenous (IV)\[^8\] and nebulized colistin (NC).\[^8\] Patients who develop VAP with MDR gram negative bacterial organisms may have better survival with adjunctive aerosolized antibiotics despite greater severity of illness.\[^8\] Aerosolized antibiotics appear to be useful in the treatment of VAP when added as adjuvants to systemic antibiotics.\[^7,8\] This is especially effective in managing drug-resistant pathogens.\[^9\] Studies have demonstrated that aerosolized antibiotics reach higher concentrations in the lung, thereby increasing their potency.\[^9,10\] From 2005, there are about 12 studies reporting the effectiveness of NC as monotherapy for VAP due to MDR.\[^11\] Although the evidence regarding aerosolized antibiotics is of low quality, that too in very selected conditions,\[^12\] the guidelines also recommend the necessity for large randomized trials to define the role of aerosolized antibiotics.

There is limited data regarding inhaled colistin for the management of VAP in postoperative pediatric cardiac patients.

The purpose of the study is to compare clinical outcomes in children treated with intravenous antibiotics with aerosolized colistin as an adjunct with those who were administered only IV antibiotics for VAP attributed to gram negative bacteria. The study also aims to evaluate the safety of inhaled colistin in this age group.

**MATERIALS AND METHODS**

**Study design and participants**

The study was carried out as a prospective, double-blinded, randomized controlled trial. The study was conducted over a period of 2 years from January 2016 to December 2017. A total of 524 pediatric patients underwent cardiac surgery during the study period.

Ninety-eight children from SICU aged less than 12 years who are mechanically ventilated and diagnosed with VAP due to gram negative bacteria in the postoperative period following cardiac surgery for congenital heart disease were included in the study. VAP was defined as per American Thoracic Society Consensus Conference criteria: by the presence of fever greater than 38°C with no other recognized cause; leucopenia (<4,000 white blood cells/mm\(^3\)) or leukocytosis (>12,000 white blood cells/mm\(^3\)); purulent tracheal secretions; and new and persistent infiltrate on chest X-ray, in patients being on mechanical ventilator support for at least 48 hours.\[^6\]

Patients who underwent emergency surgery were excluded from the study.

**Randomization and blinding**

The participants were randomized by a computer-generated algorithm to the control group (NS group) who were treated with systemic antibiotics plus nebulized sterile normal saline (NS) or the experimental group (NC group) who were administered systemic antibiotics plus NC. Both the patient and the primary physician were blinded to the nebulized drug administered.

**Ethical approval and informed consent**

After approval from the Institutional Ethics Committee, informed consent was obtained from the patient’s parents prior to the commencement of the study.

**Administration of the drugs**

In the NC group, every 12\(^{th}\) hourly, NC equivalent to 4 mg/kg of colistin base\[^6\] (1 mg = 12,500 units) reconstituted in 4 mL of sterile NS was administered immediately on reconstitution in mechanically ventilated patient via a breath-actuated jet nebulizer connected as near to the patient as possible with the patient in volume control mode and heated humidifier switched off until the nebulized solution container was empty. Similarly, in the NS group every 12\(^{th}\) hourly, 4 mL of sterile NS was given as nebulization. The patient’s primary physician was responsible for the regimen and duration of the systemic antibiotics. NC or NS was administered until the end of systemic antibiotic therapy for VAP.

Data regarding the participant demographics and other clinical parameters including vital parameters and arterial blood gas analysis were obtained from the hospital records. The Pediatric Logistic Organ Dysfunction–2 (PELOD-2) score using the European Society of Paediatric and Neonatal Intensive Care score calculator was done for every patient at the time of inclusion to the study. Each patient was clinically assessed daily until the systemic antibiotic therapy of VAP was discontinued. Microbiological culture of the respiratory specimen was aspired from the endotracheal tube on the third day.
following the initiation of treatment and once in every 7 days thereafter. Biochemical parameters including renal function tests and liver function tests were done every third day. The dosage of NC, the duration of antibiotic treatment, and any side effects related to the drug administration were noted.

Data regarding the bacteriological and clinical response of VAP were as follows:

Participant’s outcome was defined in terms of clinical and bacteriological outcomes as follows.

Clinical outcome was described as favorable when at the termination of colistin treatment presenting symptoms and signs of infection were completely or partially resolved; favorable outcome was also considered when there is normalization of white blood cell counts, improvement of arterial blood gases, and reduction or disappearance of radiological findings on chest X-ray.

Recurrence of infection was considered as any new episode of infection at least 72 hours following the clinical resolution of a preceding episode.

Bacteriological outcome of the infection was defined as follows:

Eradication – final culture of specimens demonstrating no growth of the pathogen during the entire hospitalization;
Persistence – persistent growth of the responsible pathogen regardless of the clinical outcome of the infection;
Recurrence (regrowth) – reappearance of the same pathogen regardless of the clinical outcome of the infection;
Colonization – persistence or reappearance of the same pathogen with no symptoms and signs of infection.

The duration of mechanical ventilation, the ICU length of stay, and duration of postoperative hospital stay were also recorded.

Safety parameters
Adverse effects (if any) such as bronchospasm, cough, apnea, chest tightness, and arterial hypoxemia were recorded in each participant. Also, safety was assessed on the basis of the results of renal and hepatic functions tests. Any consequent nosocomial-acquired infection, the occurrence of colistin resistance, or the development of fungal infection following administration of colistin were recorded.

The primary end point of the study was the clinical and bacteriological outcome of the VAP.

The secondary end point was the occurrence of adverse events during colistin treatment.

Statistical analysis
Data were recorded and analyzed using SPSS Version 20.0 software (SPSS Inc., California, USA). The bacteriological outcomes and the clinical outcomes were expressed as percentages. The biochemical parameters were expressed as mean ± standard deviation. Association between the clinical outcomes and the type of therapy administered was performed using Chi-square test and independent Student's t test. The association was found to be statistically significant at P < 0.05.

RESULTS
The prospective, randomized, double-blinded, controlled trial was carried out among 98 participants, of which 51 belonged to the NC group and 47 belonged to the NS group. The majority of the participants in the study were males, of which 56.8% belonged to the NC group and 59.6% belonged to the NS group [Figure 1].

There is no statistically significant difference in the mean age of the participants in the NC group (10.2 months) and the NS group (13.02 months; P = 0.591). The PELOD-2 score was 16.9 and 16.2 for NC and NS groups, respectively, which was comparable and statistically insignificant (P = 0.625) [Table 1].

The bacteriological study revealed that 25.5% of the VAP in the NC group was caused by *K. pneumoniae*, 17.6% by *Pseudomonas*, and another 17.6% by *Escherichia coli*, whereas in the NS group *K. pneumoniae* attributed to 10.6%, *E. coli* 19.1%, and *Pseudomonas* 12.9% of VAP infections. The type of organism grown in both groups is statistically comparable [Table 2].

The resistance pattern of the gram negative organisms in both the groups was plotted as a bar diagram [Figure 2].
The majority of the gram negative organisms showed resistance to augmentin (NC31 + NS32), cefoperazone–sulbactam (NC22 + NS23), piperacillin–tazobactam (NC18 + NS22), and to ciprofloxacin (NC20 + NS21).

The bacteriological outcome was studied at the end of colistin therapy. There has been eradication of the gram negative bacteria causing VAP in 80.4% of the patients in NC group and 68.1% in NS group (P = 0.16). Persistence of growth of the organism was 13.7% in the NC group and 25.5% in the NS group (P = 0.13), recurrence of the growth of the same organism was 5.9% in the NC group and 6.4% in the NS group (P = 0.9) [Table 3]. There is no statistically significant benefit of adjuvant NC on the bacteriological outcome.

The systemic antibiotics used in both NC and NS groups are colistin, antipseudomonal antibiotics such as meropenem, piperacillin–tazobactam, amikacin, tigecycline, linezolid, and cefoperazone–sulbactam. About 47.1% in the NC group and 44.6% in the NS group received both colistin along with one of the antipseudomonal antibiotic (P = 0.81), whereas 17.65 in the NC group and 38.2% in the NS group received only colistin. Rest of them received only antipseudomonal (P = 0.13). However, there is statistically no significant difference (P > 0.05) in the usage of antibiotics between the groups [Table 4].

The duration of mechanical ventilation was prolonged in the NS group (18.1 days) when compared with the NC group (11.2 days; P < 0.002). Similarly, the duration of postoperative ICU stay in the NC group was 14.04 days, whereas it was 22.3 days in the NS group, which is statistically significant (P = 0.004). The duration of hospital stay was comparatively lower in the NC group (17.6 days) compared with the NS group (26.2 days; P < 0.005) [Table 5].

There was no statistically significant difference in the occurrence of adverse effects with the use of adjunctive NC.

**DISCUSSION**

The present study is among the few randomized trials that evaluate the efficacy and safety of NC among pediatric patients in the postoperative period. VAP occurs frequently in critically ill patients resulting in significant morbidity. It is commonly associated with prolonged ventilation as a postsurgical sequela following cardiovascular surgeries. They are often considered as nosocomial infections resulting from the hospital setting. In our study, majority of the gram negative bacteria were K. pneumonia followed by Pseudomonas and E. coli. Almost all of them were multidrug resistant. In a study done by Michalopoulos and Falagas,[13] majority of the infections were attributed to Acinetobacter followed by Pseudomonas and Klebsiella. In another study done by Foglia et al.,[3] the most common gram negative...
Table 3: Comparison of bacteriological outcomes between the groups

| Parameter       | Experiment NC group (n=51) (%) | Control NS group (n=47) (%) | P   |
|-----------------|--------------------------------|----------------------------|-----|
| Eradication     | 41 (80.4)                      | 32 (68.1)                  | 0.161|
| Recurrence      | 3 (5.9)                        | 3 (6.4)                    | 0.920|
| Persistence     | 17 (33.7)                      | 12 (25.5)                  | 0.138|

NC=nebulized colistin, NS=normal saline

Table 4: Systemic antibiotic therapy among the study participants

| Characteristics                        | Experimental Control (NC) (n=51) (%) | Control (NS) (n=47) (%) | P   |
|----------------------------------------|--------------------------------------|-------------------------|-----|
| Colistin                               | 9 (17.6)                             | 18 (38.3)               | 0.062|
| Colistin + amikacin                    | 24 (47.1)                            | 21 (44.6)               | 0.862|
| Colistin + meropenem                   | 6 (11.7)                             | 8 (17)                  | 0.45 |
| Colistin + piperacillin-tazobactam     | 5 (9.8)                              | 2 (4.2)                 | 0.25 |
| Colistin + tigecycline                 | 5 (9.8)                              | 4 (8.5)                 | 0.82 |
| Colistin + linezolid                   | 1 (1.96)                             | 1 (2.1)                 | 0.9  |
| Colistin + ceftazobutax-acillin        | 2 (3.9)                              | 0                       | 0.17 |
| Colistin + trimethoprim                | 5 (9.8)                              | 4 (8.5)                 | 0.82 |
| Antipseudomonal alone                  | 18 (35.3)                            | 8 (17.1)                | 0.079|
| Meropenem                              | 5 (9.8)                              | 3 (6.3)                 | 0.53 |
| Tigecycline                            | 4 (7.8)                              | 1 (2.1)                 | 0.2  |
| Cefoperazone-sulfadiazac              | 4 (7.8)                              | 1 (2.1)                 | 0.2  |
| Piperacillin-tazobactam               | 5 (9.8)                              | 3 (6.3)                 | 0.53 |

NC=nebulized colistin, NS=normal saline

Table 5: Comparison of clinical outcome between the two groups

| Parameter                      | Mean values | P     |
|-------------------------------|-------------|-------|
|                               | Experiment NC group | Control NS group |
| Favorable (%)                 | 37          | 31    | 0.696|
| Death due to VAP (%)          | 2           | 7     | 0.073|
| Death due to other causes (%) | 12          | 9     | 0.640|
| Duration of mechanical        | 11.2        | 18.1  | 0.002*|
| ventilation (days)            |             |       |      |
| Duration of post op ICU stay (days) | 14.04   | 22.3  | 0.004*|
| Duration of postoperative hospital stay (days) | 17.6 | 26.2 | 0.005*|

*statistically significant. NC=nebulized colistin, NS=normal saline, VAP=ventilator-associated pneumonia, ICU=intensive care unit

Also, aerosolized colistin has been used successfully for prophylaxis and treatment of pneumonia caused by *P. aeruginosa* in patients with immunodeficiency virus infection.[19]

Very few studies have been done to evaluate the effectiveness of aerosolized colistin in the management of VAP in pediatric patients.[20,21] The present study aimed to examine the differences in the clinical and bacteriological outcome among patients treated with NC as an adjunctive and standard treatment of care. It was observed that the duration of mechanical ventilation, the duration of postoperative ICU stay and the duration of postoperative hospital stay were significantly lower in the group that received NC compared with the control group. The association was statistically significant (*P* < 0.05). However, there was no significant difference in the mortality between the groups. In the study done by Michalopoulos et al.[8] the addition of colistin significantly altered the attributable mortality rates. Moreover, there was a significant improvement in the clinical presentation of VAP, which is similar to the current study. Similar findings were also observed in a study published by Korbila et al.[24] where they demonstrated improved outcomes with the use of inhaled colistin in combination with IV antibiotics compared with
IV colistin alone in adult patients with VAP as a result of MDR gram negative pathogens.\textsuperscript{[17]}

The possible adverse effects of aerosolized colistin are bronchospasm, chest tightness, and apnea.\textsuperscript{[13]} However, in the current study no such adverse effects were seen. The occurrence of nephrotoxicity associated with the administration of NC was explored, and there was no statistically significant difference in the change in serum creatinine levels between the two groups ($P = 0.081$).

Aerosolized colistin may be used as a therapeutic adjunct for ventilator-associated pneumonia as it has shown minimal adverse effects.

Although aerosolized colistin in the current study has demonstrated clinically favorable outcomes, it failed to demonstrate improved bacteriological outcome. This could be due to the variations in the type of organisms grown. Another limitation of the study is the lack of availability of long-term clinical data regarding mortality and morbidity.

**CONCLUSION**

The present study has demonstrated that NC administered as an adjunct in the treatment of VAP has significant clinically favorable outcomes in terms of reduction in the duration of mechanical ventilation and reduced postoperative ICU and hospital stay in postoperative pediatric cardiac patients. Although the present study has not demonstrated significant nephrotoxicity, there is a need to exercise caution with the use of the drug, considering the age group of the patients. There is a growing need to carry out long-term exploratory research to look at the mortality and survival trends and also assess the reinfection patterns of gram negative VAP among children.

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**Conflicts of interest**

There are no conflicts of interest.

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