Efficacy and Tolerability of Nebulized 80-mg Colistin in Patients with Hospital-Acquired Pneumonia and Ventilator Associated Pneumonia Caused by *Acinetobactor baumannii*

นิพนธ์ต้นฉบับ

Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินผลลัพธ์ทางคลินิก ผลลัพธ์ทางจุลชีววิทยา และความปลอดภัยของการใช้ยา colistin แบบพ่นเสริมกับยาฉีดในการรักษาปอดอักเสบโรงพยาบาล (HAP) หรือ ปอดอักเสบจากการใส่ท่อช่วยหายใจ (VAP) ที่เกิดจากเชื้อ *A. baumannii*. **วิธีการศึกษา:** เป็นการศึกษาแบบย้อนหลังในผู้ป่วยที่ได้รับยา colistin แบบพ่นในขนาด 80มิลลิกรัม ทุก 8 ชั่วโมง เสริมกับยาฉีดในการรักษาปอดอักเสบโรงพยาบาลหรือปอดอักเสบจากการใส่ท่อช่วยหายใจที่เกิดจากเชื้อ *A. Baumannii* ณ โรงพยาบาลมหาราชนครเชียงใหม่ ระหว่างเดือนพฤษภาคม พ.ศ. 2556 ถึง เดือนมิถุนายน พ.ศ. 2558 **ผลการศึกษา:** ผู้ป่วยจำนวน 107ราย ที่เข้าร่วมการศึกษาตรงเกณฑ์การคัดเข้ามีผลลัพธ์ทางคลินิกที่ดี 69 ใน 107 ราย (ร้อยละ 64.49) พบว่าสามารถกำจัดเชื้อได้หลังจากสิ้นสุดการรักษาเป็น 94 ใน 107 ราย (ร้อยละ 87.85) นอกจากนี้พบอาการหลอดลมหดเกร็งร้อยละ 6.54 และเกิดพิษต่อไตร้อยละ 40.19 ตามลำดับ **สรุป:** ยา colistin ขนาด 80 มิลลิกรัมแบบพ่นทุก 8 ชั่วโมง อาจใช้เสริมกับยาฉีดในการรักษาปอดอักเสบโรงพยาบาลหรือปอดอักเสบจากการใส่ท่อช่วยหายใจที่เกิดจากเชื้อ *A. baumannii* ได้ อย่างไรก็ตาม ยังต้องการการศึกษาที่ใหญ่ขึ้น รวมถึงมีกลุ่มควบคุมเพื่อยืนยันถึงประโยชน์ที่จะได้รับจากการใช้ยาพ่นเสริมดังกล่าว

คำสำคัญ: โคลิสติน, การพ่นละออง, *A. baumannii,* โรคปอดอักเสบโรงพยาบาล, โรคปอดอักเสบจากการใส่ท่อช่วยหายใจ

Abstract

Objectives: To evaluate clinical outcome, microbiological outcome and tolerability of adjunctive colistin nebulization in *Acinetobactor baumannii* hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). **Materials and methods:** This retrospective study included patients receiving 80 mg colistin nebulization given every 8 hours adjunctive to IV colistin for treating *A. baumannii* HAP or VAP, admitted to Maharaj Nakorn Chiang Mai Hospital between May 2013 and June 2015. **Results:** One hundred and seven adult patients who met inclusion criteria were recruited. Favorable clinical outcome of treatment was observed in 69 of 107 patients (64.49%). The microbiological eradication rate was 87.85% of all cases. Owing to tolerability, bronchospasm and nephrotoxicity were 6.54% and 40.19%, respectively. **Conclusion:** Colistin nebulization with a dose of 80 mg given every 8 hours could be used as an adjunctive therapy to the intravenous colistin in treating patients with *A. baumannii* HAP or VAP. However, studies with a larger sample size and well-controlled group are required to adequately address the benefits of colistin nebulization.

Keywords: colistin, nebulization, *A. baumannii*, hospital-acquired pneumonia, ventilator-associated pneumonia

Introduction

Pneumonia is the most common nosocomial infection (NI) in Thailand. In a nationwide study of Danchaivijitr and colleagues in August 2006, they found that lower respiratory tract was the mostly found NI.[1] Patients with pneumonia need more mechanical ventilation and have a high morbidity and mortality, especially those with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Werarak et al revealed that the 30-day mortality rates among patients with either HAP or VAP were up to 45.9%, equally.[2] Even with high unfavorable outcomes, the optimized antimicrobial practice in drug resistant era has been difficult to achieve, particularly the practice to tackle the multidrug resistant *Acinetobactor baumannii*.[3]

A. baumannii, a gram negative coccobacillus, is the most causative pathogen of nosocomial pneumonia.[4] Reechaipichitkul et al[5] and Werarak et al[2] reported that *A. baumannii* was the mostly found organism in VAP patients. Multi-mechanisms of antimicrobial resistance of *A. baumannii* could be attributable for various mechanisms including drug-destroying enzymes (especially carbapenemases), porin loss, efflux pump, and changes or reductions of penicillin-binding proteins.[3,6] In the multi-drug and pan-drug resistance era, colistin is the best treatment option for antimicrobial

resistance.[3] However, colistin does not fairly distribute into epithelial lining fluid.[7] Thus, colistin nebulization was applied as an adjunct to systemic therapy. To date, nebulization of colistin has been increasingly used in clinical practice.[8]

In patients with *A. baumannii* HAP or VAP that is sensitive only to colistin, the recommended treatment is intravenous colistin monotherapy or adjunctive inhaled colistin.[9] This is recommended by the last update on management of adults with HAP and VAP, endorsed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS).[9] Additionally, a recent meta-analysis showed that aerosolized colistin is associated with an improvement in clinical response, microbiological eradication, and infection-related mortality in treating VAP.[10]

As multi-drug resistance has been found more frequently in higher levels of healthcare setting, Maharaj Nakorn Chiang Mai Hospital, a university hospital in northern Thailand, is no exception. The problem of antimicrobial resistance has been constantly increasing. Chaiwarith et al found that there were 48 isolates (46% of all isolates) of pan-drug resistant *A. baumannii* of which, at the time of the study, it was resistant to all available antibiotics except for colistin and tigecycline.[11] Inchai and colleagues reported that the major causative pathogen among VAP patients was *A. baumannii* (54.3%) which comprised 90% of the drug-resistant strains.[12] Because of a high rate of *A. baumannii* pneumonia, nebulized colistin with a usual dose of 75 mg of colistin base (given every 12 hours until systemic antibiotic therapy for VAP was ended) has been considerably heavily used in the institution. Such dosage regimen of 75 mg of nebulized colistin given every 12 hours however offers unclear benefit as suggested by a clinical trial by Rattanaumpawan and colleagues (2010).[13] The study found that the favorable clinical outcome between colistin group and control group was not different (51.0% and 53.1%, respectively, P = 0.84) even though microbiological outcome in colistin group (60.9%) was superior to that in control group (38.2%) with a statistical significance (P = 0.03).[13] There has been no data indicating whether a higher dose of adjunctive aerosolized colistin could offer a clinical outcome better than the usual dose in Thailand. Therefore this study aimed to assess clinical outcome, microbiological outcome, and tolerability of adjunctive colistin nebulization (80 mg given every 8 hours) in *A. baumannii* HAP or VAP. Our results could be useful in supporting antibiotic aerosolization in the era of pathogens sensitive only to colistin.

Materials and Methods

This retrospective study included patients with HAP or VAP who were admitted to Maharaj Nakorn Chiang Mai Hospital, a 1400-bed teaching hospital in Chiang Mai province, Thailand, between May 2013 and June 2015. The protocol was approved by the ethics committee of the Faculty of Medicine, Chiang Mai University, with a waiver for informed consent (Study Code: NONE-2558-02810).

Participant verification

To verify eligible participants, definitions of pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia were as follows. According to the IDSA/ATS practice guideline 2005, diagnosis of pneumonia was based on clinical criteria which include the following: 1) systemic inflammatory syndrome as indicated by at least 2 of 4 signs (body temperature > 38 °C or < 36 °C, respiratory rate > 20 beats per minute, heart rate > 90 beats per minute, and white blood cells > 12,000 cells per mL or < 4,000 cells per mL), 2) clinical symptoms (cough, purulent sputum, or pleuritic chest pain), and 3) evidence of new or persistent infiltrate seen on chest radiography. *Hospital-acquired pneumonia (HAP)* was defined as pneumonia in a patient hospitalized for more than 48 hours. *Ventilator-associated pneumonia (VAP)* was defined as pneumonia in a patient after using a mechanical ventilator for more than 48 hours.[11-14] Discrepancy between the doctor's definite diagnosis and the criteria mentioned above was checked and resolved.

Outcomes ascertainment

To decide the clinical outcomes, we defined the following criteria. While clinical cure was defined as a complete resolution, clinical improvement was defined as a partial resolution, of signs and symptoms of the infection at the end of antibiotic therapy. Favorable outcome was a composite outcome of either clinical cure or clinical improvement. In addition, failure patients were those whose clinical symptoms were worse or their antimicrobial agent had to be changed or added. Finally treatment failure was defined as either the failure as mentioned previously or death.

Microbiological outcome was defined as one of the four categories including eradication, presumed eradication,

presumed persistence, and persistence. Eradication was defined as an elimination of *A. baumannii* from the lower respiratory specimen. Presumed eradication consisted of an absence of the result of culture coupled with clinical improvement after *A. baumannii* strain was initially isolated. Presumed persistence was defined as an absence of the result of culture coupled with clinical deterioration after *A. baumannii* strain was initially isolated. Finally, persistence was designated as a failure to eradicate *A. baumannii*. In terms of composite outcomes, successful microbiological response referred to either eradication or presumed eradication. Failed microbiological response was referred to either presumed persistence or persistence.

Regarding the safety, tolerability of the regimen was defined as an absence of bronchospasm reaction to nebulized colistin in the entire course of treatment. For nephrotoxicity, the severity of acute kidney injury was evaluated by the RIFLE criteria which differentiates five grades of renal insufficiency, namely risk, injury, failure, loss of function, and end-stage renal disease.[15] Patients with any RIFLE grade was considered having acute kidney injury. The Simplified Acute Physiology Score (SAPS II) for each patient was calculated as guided by Le Gall and colleagues (1993).[16]

Participant inclusion

The inclusion criteria for participants in this study consisted of the age of 18 years or older, having diagnosed with pneumonia either HAP or VAP that was compatible with the definitions described previously, and receiving the adjunctive colistin 80-mg nebulization every 8 hours for A. baumannii HAP or VAP for at least 2 days. Transferred patients and patients whose data in the medical record were incomplete were excluded.

Data collection

Data were extracted from medical records. Demographic information included age and gender; while clinical information consisted of underlying disease, type of medical ward, mechanical ventilator use, septic shock status, hepatic function, renal function, immune status, intravenous antimicrobial regimen, reported antimicrobial susceptibility, duration of HAP or VAP treatment, and the study clinical outcomes as described previously.

Statistical analysis

Descriptive statistics was used to present participants' characteristics and clinical status. Continuous variables such as age and SAP II score were reported as mean with standard deviation (SD); while categorical variables, such as ICU admission, gender, underlying disease, sepsis/septic shock, antibiotic regimen, clinical outcomes, microbiological response, and adverse drug reaction were reported as frequency with percentage. Median with interquartile range was used as appropriate. All statistical analyses were done using Stata® software, version 14 (Stata-Corp, College Station, TX).

Results

One hundred and seven adult patients received aerosolized colistin as the adjunctive treatment for the management of HAP and VAP caused by *A. baumannii* (Table 1). There were more men (68 of 107 patients, or 63.55%) than women (39 or 36.45%). Their mean age was 64.61 ± 17.98 years. Clinically, participants had a mean SAPS II score obtained on the day of hospital admission of 46.85 ± 11.82. The median duration of inhalations of colistin was 11 ± 7 days.

Table 1 Demographic and clinical characteristics of participants (N = 107).

Characteristics	N (%)
Age (years) [mean±S.D.]	64.61 ± 17.98
Gender	
- Female	39 (36.45)
- Male	68 (63.55)
Length of stay (days) [median (IQR)]	30 (21)
ICU admission	34 (31.78)
SAP II score[a] (mean±S.D.)	46.85 ± 11.82
Underlying disease	**90 (84.11)**
- Cardiovascular disease	61 (57.01)
- Diabetes mellitus	30 (28.04)
- Chronic kidney disease	24 (22.43)
- COPD	8 (7.48)
- Malignancy	18 (16.82)
- Others	43 (40.19)
Sepsis/Septic shock	57 (53.27)
Duration of neubulized colistin (day) [median (IQR)]	11 (7)
Concomitant drug therapy	
- Colistin (5 mg/kg/day)	106 (99.07)
- Vancomycin (30 mg/kg/day)	42 (39.25)
- Rifampicin (600 mg/day)	4 (3.74)
- Amikacin (15 mg/kg/day)	2 (1.87)
- Acyclovir (10 mg/kg q 8 hr)	4 (3.74)
- Amphotericin B (0.7 mg/kg/day)	1 (0.93)

S.D. = standard deviation; ICU = Intensive Care Unit; SAP = Simplified Acute Physiology score.
[a] SAP II score obtained on the day of admission to the hospital.

In terms of clinical outcomes, the majority of the participants had clinical improvement (50.47%), followed by

clinical failure (35.51%) and clinical cure (14.02%). As a result, 64.49% had a favorable outcome. For the microbiological outcomes, eradication was found in 87.85% and failure was in the rest 12.15%. Regarding adverse effects, bronchospasm was found in 6.54% of the participants. However, acute kidney injury occurred in as high as 40.19% of the participants.

Table 2 Clinical outcome, microbiological response and adverse drug reaction among *A. baumannii* HAP or VAP (N = 107).

Outcomes	N (%)
Clinical outcome	
- Cure	15 (14.02)
- Improvement	54 (50.47)
- Failure	38 (35.51)
Clinical response	
- Favorable outcome	69 (64.49)
Microbiological outcome	
- Eradication	94 (87.85)
- Failure	13 (12.15)
Adverse drug reaction	
- Bronchospasm	7 (6.54)
- Acute kidney injury	43 (40.19)

Discussions and Conclusion

Our retrospective study examined the outcome of 80-mg nebulization every 8 hours for *A. baumannii* HAP or VAP for at least 2 days. At the end of the treatment, the favorable outcome, which was a composite outcome of clinical cure or clinical improvement, was about 65%. Our finding on favorable outcome was superior to that in the study of Rattanaumpawan and colleagues (2010).[13] of which they found a 51.0% in colistin group and 53.1% in control group (normal saline solution). They studied the regimen of 75 mg of nebulized colistin given every 12 hours. This could suggest that a high dose of nebulized colistin offers a higher rate of clinical outcome than the usual dose. However, the interpretation should be with caution since our study, with its retrospective in design, did not have a control group to account for a certain level of bias.

The efficacy of IV colistin the treatment of HAP or VAP has been questioned because of its limited penetration into lung parenchyma. Aerosolized colistin as an adjunct to IV administration is a suitable option because it achieved a higher pulmonary concentration than the IV administration. However, the best route of colistin administration remains unclear.[17] According to its last update, the IDSA guideline recommends that for patients with VAP due to gram-negative bacilli that are susceptible to only colistin, both inhaled and systemic antibiotics are recommended, rather than systemic antibiotics alone. Thus, information about optimal delivery and dosage with regard to inhaled antibiotic therapy is needed.[9]

The dosage of aerosolized colistin recommended in the UK is 16 mg of colistin base activity (CBA) every 12 hours for patients with body weight < 40 kg and 33 CBA every 12 hours for those with body weight > 40 kg.[18] However, the pharmacokinetic study of inhaled colistin in mechanically ventilated critically ill patients has shown that a dose of 33 CBA every 8 hours was inadequate to treat multidrug-resistant strains. It could be that lower doses of colistin could not offer an adequate concentration in the lung.[19] The dose in our study, 80 mg every 8 hours, was about two to three times higher than those previously reported.

In the present study, we found that our favorable clinical outcome of 64.49% was loosely similar to that obtained by Lu et al[20] who achieved a clinical cure rate of 66%. Specifically their clinical cure consisted of resolution of clinical outcome and biological sign of infection, and negative cultures.[20]

However, the microbiological outcome of eradication in our study (87.85%) was higher than 37.8% in a study by Chih Lin et al[21], a retrospective study established in patients treated with aerosolized colistin for VAP due to MDR *A. baumannii*. Better microbiological outcome in our study could be attributable to a daily dose (240 mg CBA) higher than the one in their study (143 mg CBA).[21] Their lower daily dose was possibly insufficient for the additional therapeutic value.

The main adverse effect of IV colistin treatment is acute kidney injury. In our study, the incidence of acute kidney injury (40.19%) was higher than that found by Michalopoulos et al. [22] They reported a nephrotoxicity incidence of 15.7% upon using IV 300 mg CBA per day which is similar to the dose in our study. With an identical daily dose, nebulization dosage form could potentially have caused less acute kidney injury than the IV form; our finding was unexpected. Such unexpected finding could be attributable to the discrepancy of the definition of nephrotoxicity. In our study, the RIFLE criteria were used; while the study of Michalopoulos et al defined nephrotoxicity as a doubling of the baseline serum creatinine level.[22]

In the present study, bronchoconstriction (6.54%) was slightly higher than 4.7% in the study of Kwa et al.[20] This could be in part due to a dose of aerosolized colistin in our study (80 mg CBA every 8 hours) which was higher than 33 mg CBA twice daily in their study.[23] The incident in our study was somewhat comparable, if not obviously much better, to 7.8% found in the work of Rattanaumpawan et al with a smaller dose of 75 mg CBA twice daily.[13]

Our study had some limitations. Firstly, as a retrospective study, confounders were of great concerns. These included but not limited to the development colistin-resistant pathogens during treatment, nebulization technique, and the changing MIC of colistin). Secondly, with no control group, i.e., patients with *A. baumannii* HAP and VAP receiving only intravenous colistin, a more comparable incident rate of the current standard treatment could not be determined. Thus the incidents of clinical and microbiological outcomes could be overestimated. In addition, most patients also received intravenous colistin (99.07%) that could have influenced the favorable clinical outcomes. Our findings thus could be more properly generalized to the identical treatment modality, i.e. nebulized plus IV colistin.

In conclusion, 80 mg colistin nebulization every 8 hours as an adjunctive to IV colistin at a standard dose (5 mg/kg/day, maximum dose of 300 mg/day) in the treatment of HAP and VAP due to *A. baumannii.*

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Editorial note
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