Polymyxins Nebulization over Intravenous Injection: Pharmacokinetics and Pharmacodynamics-based Therapeutic Evaluation

Abstract

Polymyxins are the last line potential antibiotics against multi-drug resistant gram-negative bacteria and consist of two sister antibiotics: polymyxin B and colistin (polymyxin E). Intravenous use of polymyxins was started from a long ago in the treatment of serious gram-negative infections and once their uses were restricted due to potential adverse drug reactions, such as nephrotoxicity and neurotoxicity. Lack of *in vivo* clinical studies on polymyxins mostly, in human body makes the pharmacokinetics and pharmacodynamics of polymyxin B and colistin unclear in many aspects, such as the distribution of polymyxins in different compartments of lung. The nebulization of polymyxins is practicing very limitedly and lack of clinical evidence has not justified this administration technique yet properly to date. The main objective of this review study was to evaluate the pharmacokinetic and pharmacodynamic properties of intravenous and nebulized polymyxins and the related therapeutic potentialities. Aerosolized polymyxins directly administered to the respiratory tract was found with higher drug concentration in different subcompartments of lungs than the intravenous administration and sustainably meets the minimum inhibitory concentration locally with superior bactericidal properties in respiratory tract infections. In contrast, intravenous administration of polymyxins shows similar anti-infective superiority in other organs,

such as blood, urinary tract etc. So, during this alarming situation of rapidly emerging multidrug-resistant organisms in human communities, therapeutic administration techniques of last resort polymyxins should be clinically evidence-based for achieving optimum therapeutic outcomes with minimum chance of adverse drug reactions.

Keywords:

Polymyxins; Nebulization: Intravenous; Pharmacokinetics; Pharmacodynamics

1. INTRODUCTION

Infections caused by multidrug-resistant (MDR) gram-negative bacteria are considered as a threat for global human health and in most of cases, have c vbeen associated with extremely poor therapeutic outcomes. At present, the emergence of gram-negative bacteria those are capable of producing extended spectrum β-lactamases, metallo-β-lactamases and carbapenemase, is the vital alarming issue for the infectious diseases scientists and experts, globally [1]. MDR pathogen, carbapenem-resistance *enterobacteriaceae* (CRE) is found as the most detrimental gram-negative bacteria in all global human-communities and CRE-associated infections are accompanied with high rated mortality and increased hospital staying-cost, and also the most difficult infections to treat [2, 3]. In the 1940s, a potential polypeptide group of antibiotics, called polymyxins, was discovered, and polymyxin B and colistin (also known as polymyxin E), belongs to polymyxins-group, was initiated to clinically use against those gram-negative bacteria. Intravenous polymyxins were clinically used for at least two decades after its

invention. After that, due to the increased number of polymyxins-induced renal and neuro toxicities, the uses of polymyxins were restricted, globally [4-9].

Among the few last resort potential antibiotics against MDR-CRE, both polymyxin B and colistin are the most prosperous and effective antibiotics. In regards of pharmacokinetics (PK) and pharmacodynamics (PD), intravenous polymyxin B and colistin shows variable characteristics to each other, and controversies are all-around regarding their dosing with limited clinical evidences [4, 6, 10]. The dose versus distribution of intravenous polymyxin B and colistin in respiratory tract is still an unjustified issue, and intravenous form is associated with increased incidences of adverse events [11, 12]. However, in recent years, as a new alternative effective treatment option of MDR-CRE-associated infections, inhalation therapy of polymyxins is found with higher potentiality than intravenous therapy, but the study data is too limited to justify [13, 14]. The main objective of this review study is to evaluate the latest clinical outcomes of nebulization therapy of polymyxin B and colistin considering their PK and PD properties.

2. STRUCTURE, MECHANISM OF ACTION AND SPECTRUM OF ACTIVITY

Polymyxins are cationic polypeptides that contain a cyclic heptapeptide having a tripeptide side chain where N terminus is completely acylated by a fatty acid tail [10]. Amino acid components in the peptide chain basically differentiate between polymyxin B and colistin. L-threonine and L-αγ-diaminobutyric acid (Dab) is common in both

antibiotics but, the only difference is that polymyxin B contains D-phenylalanine whereas, in the same position, colistin possesses D-leucine [1, 10].

Polymyxin B is the active form of drug and administered directly while colistin is the bio-active form an inactive prodrug, colistimethate Sodium (CMS) [10]. Polymyxins increase cell membrane's permeability of the gram-negative bacteria by displacing Ca^{2+} and Mg^{2+} from PO_4^{3-} of the bacterial cell membrane through an electrostatic interaction between $\alpha\gamma\text{-}Dab^{+}$ of polymyxins and PO_4^{3-} of the bacterial cell membrane, and finally, bacterial cell death takes place (Fig. 1) [1, 10].

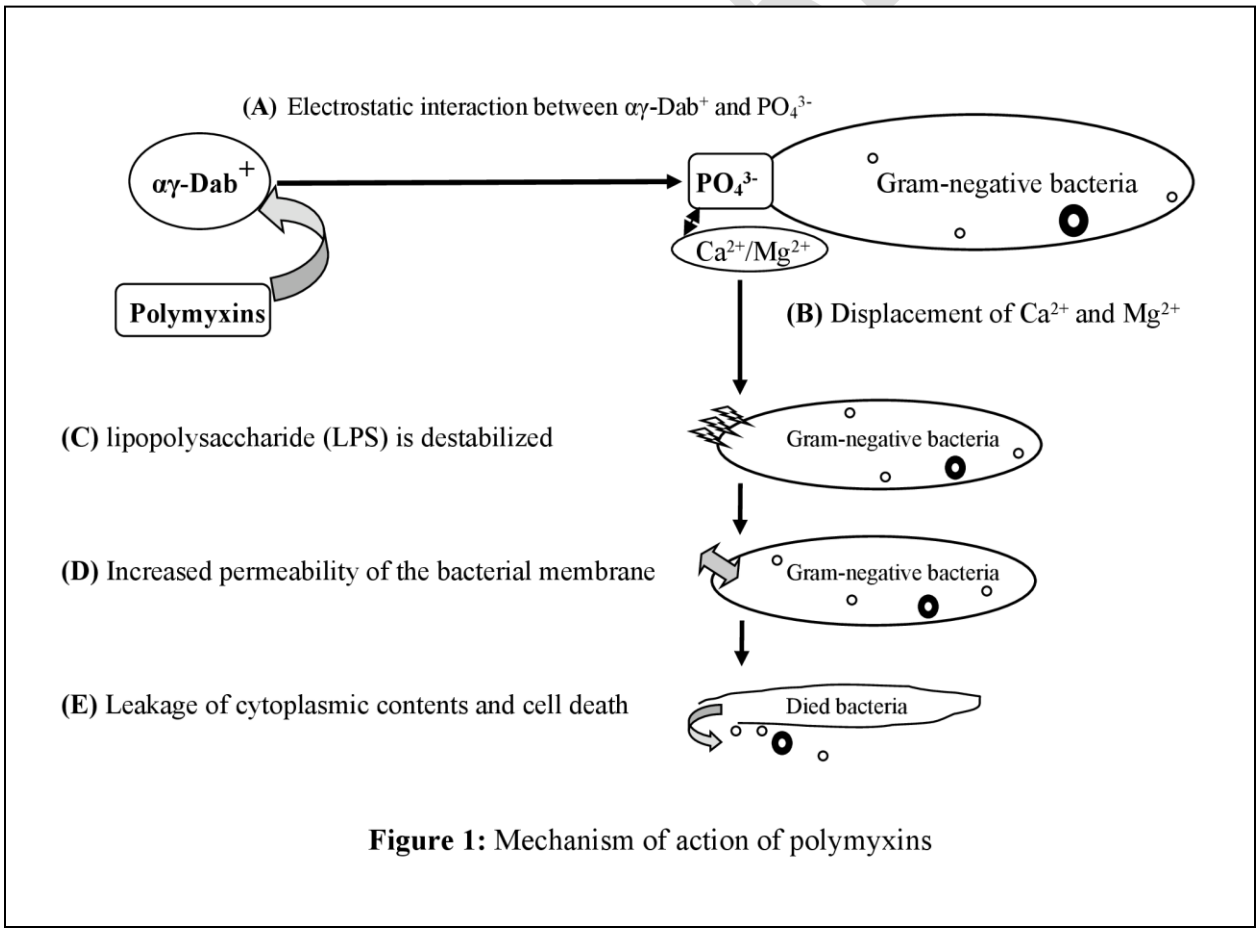

Figure 1: Mechanism of action of polymyxins

Polymyxins have narrow spectrum bactericidal property against common gram-negative bacteria and prominent activity is found against the most members of *Enterobacteriaceae* family, such as *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia.* Some gram-negative bacteria are naturally resistant to polymyxins like, *Serratia marcescens, Proteus* spp., *Burkholderia cepacia, Morganella morganii, Campylobacter, Providencia* spp., *Brucella*, *Legionella*, *Edwardsiella* spp. and *Vibrio cholera* [10, 15].

3. DOSING: IV Injection and Nebulization

Polymyxin B is commercially available as intravenous polymyxin B sulfate and colistin has to commercial forms; colistimethate sodium (CMS) is intravenously used while colistin sulfate is used topically or orally [1]. The commercial package of polymyxin B expresses its strength in International Unit (IU) and 10,000 IU is equal to 1 milligram of polymyxin B. In healthy renal function, the recommended intravenous daily dose of polymyxin B is 15,000-25,000 IU/kg of body weight (BW) (1.5–2.5 mg/kg of BW) divided into 2 equal doses for adults and children older than 2 years. Standard dose adjustment guideline either in renal impaired patient or in patient with intermittent hemodialysis or continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF) has not yet been established [16]. As a prodrug, CMS is commercially available in million and milligram, but after intravenous administration, CMS is converted in the biological system to colistin base activity (CBA) which is the pharmacologically active form (conversion: 1

million international unit CMS = 80 mg CMS = 33 mg CBA). For resolving the dosing conflicts of CMS, 'Million International Unit' (MIU) is the globally most preferred unit of expression [17-19]. The usual daily recommended dose of intravenous CBA is 75-600 mg (through intravenous route in the form of CMS) and alternatively, 2.5-5 mg/Kg of BW divided into 2 to 4 equal doses [19, 20]. Dose adjustment is recommended in renal impairment. As per the practice guidelines in United States (US), in serious gram-negative bacterial infections in adults and children, CMS 2 MIU in every 12 hours, 24 hours and 36 hours is recommended in serum creatinine level 1.3-1.5 mg/dL, 1.6-2.5 mg/dL and ≥2.6 mg/dL, respectively [1, 20]. In the United Kingdom (UK), the daily dosing regimen of CMS has been upgraded to 4-6 mg/Kg of BW (50,000-75,000 IU/kg of BW) divided into 3 equal doses, in adult and children with normal renal function [20, 21]. Colistin is significantly removed during intermittent hemodialysis and supplementary dosing of CMS is required after each dialysis session to maintain steady serum CBA concentration [20, 21].

Direct administration of polymyxins in gram-negative bacteria-associated respiratory tract infections (RTI) is restricted, such as colistin nebulization in patients with cystic fibrosis [10]. The aerosolized dosing regimen of polymyxin B and colistin has not yet been globally established and in some places, recently this drug delivery system has been introduced as a secondary administrative option for treating serious infections of RTI. Due to the lack of PK/PD data on aerosolized polymyxin B, no specific dosing regimen has yet been developed [23]. In a 18-month long ICU-based study, researchers found that polymyxin B nebulization in 2 mg/Kg of BW/ day in 2 equally divided doses

showed promising therapeutic outcomes [13]. In the UK, the recommended aerosolized dosing regimen of CMS is 500,000 units (40 mg CMS) every 12 hours for patients with a BW ≤40 kg and for a BW >40 kg, the dose is 1 MIU (80 mg CMS) every 12 hours. The highest recommended dose is 2 million units (160 mg CMS) every 8 hours, especially in recurrent severe RTI [1, 22].

4. PHARMACOKINETICS: IV INJECTION AND NEBULIZATION

The pharmacokinetics of polymyxins is not clearly understood to date with limited number of clinical studies. One study included 8 critically ill patients and found that <1% of administered polymyxin B is excreted through urine as unchanged form and the major portion of the dose is extensively reabsorbed from the renal tubules, and eliminated through non-renal pathway [24]. Thus, limited renal function does not affect the serum steady state concentration (C_{ss}) of polymyxin B [10]. Another study was conducted on 24 critically ill patients with mild to severe renal impairment (CL_{Cr}= 10–143 mL/min). Intravenous polymyxin B dose was given as 0.45 mg/kg of BW/day - 3.38 mg/kg of BW/day and researchers estimated the $C_{ss,avg}$ was 0.68 mg/L - 4.88 mg/L and only 4.04% (median value) was recovered in urine [25]. That study included 2 patients with continuous renal replacement therapy (CRRT) where 5.62% and 12.2% of the administered dose was removed as dialysate during the dialysis [25]. Hence,

supplementary dosing of polymyxin B is required for patients with CRRT but, lack of specific clinical study, the supplementary dose of polymyxin B has not yet been established [25, 26]. Following the intravenous administration of CMS, the major portion of CMS is eliminated by kidneys and high concentration of CMS becomes available in urine [27]. Only 20-25% of a CMS dose is hydrolyzed into active colistin before it passing through glomerulus and renal tubules and a relatively smaller fraction of total CMS dose is found in the system to provide its antibacterial action [28]. This colistin is extensively reabsorbed in the renal tubules and eliminated predominantly through the non-renal pathway [10]. During passing through the urinary tract, CMS is also converted to colistin, reabsorbed and negligible amount is excreted by urine [28]. Thus, it is difficult to achieve a $C_{ss,avg}$ of 1 mg/L in healthy renal patient followed by a usual CMS dosing [29]. Due to excessive removal of CMS during from body during hemodialysis, a supplementary dose 1.7 million IU of CMS is required to replenish the loss [26].

The distribution of polymyxin B in extravascular sites following intravenous administration is little known due to lack of *in vivo* studies. A study was conducted on Sprague-Dawley rats and analyzed the different tissue concentrations followed by an intravenous polymyxin B dose of 3 mg/kg of BW. Highest polymyxin B concentration was detected in the proximal renal tubular cells. Higher concentration was also found in lung tissue than the serum at 6 h but, variable drug-distribution pattern was observed in different subcompartments of lung, such as lung parenchyma, alveolar epithelium, epithelial lining fluid and so on [30]. A study found that followed by a usual intravenous dose of CMS, a minimal level of colistin is found in sputum in patients with cystic fibrosis (CF). The penetration of colistin in the central nervous system through blood-brain

barrier is very poor (approximately 5%) [31], and during meningitis and inflammation, it ranges from 25% to 67% [32, 33] and even no concentration detected [34]. Distribution of colistin to biliary tract, different joint fluids and pleural fluid is also poor [35]. A study on 13 critically ill patients found that suboptimal serum concentration and undetectable concentration of colistin in bronchoalveoalar lavage fluid is attained followed by intravenous 480 mg CMS/day [36].

Polymyxins nebulization is a new technique of delivering aerosolized polymyxins directly at the site of infection specially, in the respiratory tract. Lack of dependable pharmacokinetic and pharmacodynamic data basically makes this method to date unpopular [26]. The first clinical evidence of aerosolized polymyxin B administration directly to the respiratory tract was recorded in 1695. In that case study, recurrent presence of *Pseudomonas aeruginosa* in the sputum after treating with intravenous polymyxin B, aerosolized polymyxin B was administered directly with few therapeutic success [37]. A study was conducted to analyze the pharmacokinetics and pharmacodynamics of aerosolized polymyxin B in neutropenic mouse lung infection model (infected with *Pseudomonas aeruginosa*), after inhaling polymyxin B (dose: 4.12 and 8.24 mg base/kg of BW; volume of 25 µL). The post 24-hour histopathological analysis found a comprehensive result in the reduction of infection (AUC/MIC: R^2= 0.70 to 0.88) in lung of mice and that included lung epithelial integrity. The same study also showed effective PK/PD characteristics attained by polymyxin B nebulization and achieved relatively higher drug concentration than intravenous polymyxin B [23]. The concentration of polymyxin B is affected by the route of administration and relatively higher concentration is attained by inhaling polymyxin B in mice [23].

Similar kind of advantageous results were found with colistin nebulization in MDR gram-negative pathogens-associated RTIs. A study on 21 patients found 85.7% microbiological response and 57.1% therapeutic response when nebulized colistin was applied against MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa*-associated pneumonia [14]. A recent study found that the concentration of colistin in sputum of patients with CF is minimally followed by intravenous CMS administration. When aerosolized colistin was administered, a >10-fold higher concentration (dose of CMS: 4 MIU/day) of colistin was found in sputum [38]. In a rat PK study, 23-39% of the pulmonary administered CMS dose was converted to active colistin in the rat lung [39]. This CMS to colistin conversion is a slow process and the highest concentration of colistin achieved after 1 to 5 hours of CMS nebulization in patient with CF [38]. However, few specific clinical studies are required at this moment to understand the real therapeutic and microbiological outcomes of polymyxins nebulization in patients with MDR gram-negative bacteria-associated RTIs.

5. PHARMACODYNAMICS: IV INJECTION AND NEBULIZATION

Colistin is widely used in several clinical studies for analyzing the overall pharmacodynamic properties of polymyxins including polymyxin B [26, 40-42]. Multiple *in vitro* studies showed that colistin possesses a rapid concentration-dependent killing property against the MDR gram-negative bacteria and a short post-antibiotic effect followed by achieving even maximum serum colistin concentration [40-42]. *A. baumannii, K. pneumonia and p. aeruginosa* are the furious resistance developing

organisms, and both polymyxin B and colistin shows a rapid killing phenomenon against these organisms but a rapid re-growth property is observed in these organisms [43-45]. In neutropenic mouse thigh and lung infection models, the antibacterial property of colistin against *A. baumannii* and *P. aeruginosa* is predicted nicely by using PK-PD index which is the ratio of the area under the unbound (free) drug concentration-time curve at 0-24 hours to the MIC (minimum inhibitory concentration) ($fAUC_{0–24}$/MIC); considering the PK/PD index which is superior to the maximum serum drug concentration (C_{max})/MIC relationship, it is suggested that time versus colistin exposure in the serum is more effective than achieving a maximum (peak) serum colistin concentration [10, 26, 46]. To maximize the killing ability of colistin, the average steady-state plasma colistin concentration should be maintained at 2 µg/mL [47]. Heteroresistance of MDR *K. pneumonia* [48], *P. aeruginosa* [49] and *A. baumannii* was found against colistin in 23-100% of clinical isolates [50, 51].

Most of the clinical studies were associated with intravenous polymyxins administration and pharmacodynamic properties of polymyxins are mostly based on those clinical data. The use of colistin nebulization in patients with *P. aeruginosa*-associated CF is an oldest practice [52, 53]. A study on neutropenic infected mice showed that nebulized polymyxin B increases the total exposure time and this extended pulmonary exposure of polymyxin B is maintained above the resistance breakpoints >2 mg/L over 12-hour against *P. aeruginosa* and *A. baumannii* [54]. The strong molecular binding of polymyxin B to the alveolar macrophages [55] and the alveolar basement membrane is the main fact behind the longer retention time of polymyxin B in epithelial lining fluid (ELF) [56].

Same prolonged and extensive retention of colistin was observed in studies on sheep, rats, and mice [57-59].

6. NEBULIZATION VERSUS IV INJECTION: THERAPEUTIC OUTCOMES AND SAFETY

Experience with intravenous polymyxins mostly, with colistin to date is abundant but, very negligible with polymyxins nebulization. A cohort study was experienced with significantly inferior clinical response (25%) when 60 patients of that study were treated with intravenous colistin for treating pneumonia associated with MDR *P. aeruginosa* and *A. baumannii* [60]. The main reason behind that less favorable outcome in that study was the intravenous administration of colistin which might be responsible for inadequate achieved concentration of colistin in ELF of the pulmonary parenchyma [60]. Some similar kind of studies found anecdotal clinical outcomes with colistin nebulization in 3 patients [61] and 8 patients [62]. Furthermore, renal dysfunction is the most frequently experienced adverse event associated with intravenous colistin therapy in usual doses [14, 60]. Another study with 21 patients suffering from MDR *A. baumannii* and *P. aeruginosa* strains-associated pneumonia was experienced with favorable clinical outcome (85.7%) and no renal dysfunction, significantly with the nebulization therapy of colistin [14]. A recent clinical study on 60 patients with pneumonia treated with intravenous polymyxin B in combination therapy, showed 20% mortality and 88% cure rate [63]. Only one study was conducted to evaluate the PK/PD of polymyxin B administration in intravenous (dose: 2 mg/Kg) versus nebulization (dose: 2 mg/Kg)

route, in MDR pneumonia patients. That study found superior clinical outcomes in terms of disease improvement, cure and failure rates, with polymyxin B nebulization (44%, 44% and 12%, respectively) in comparison to intravenous administration (40%, 20% and 40%, respectively) [13]. Multiple studies found 16% (bronchospasm) [13] and 21% adverse event when aerosolized polymyxin B was administered [64]. Study showed nephrotoxicity occurred 28% with intravenous administration while no adverse event was recorded against nebulization of polymyxin B [13]. Critically ill patients in ICU, commonly suffer from multiple drug-associated nephrotoxicity those are difficult to detect and intravenous polymyxins may aggravate this possibility [13]. Polymyxin B nebulization therapy reduces the overall hospital staying time (28.68±9.15) more than intravenous therapy (31.64±9.16) (p-value: 0.258786) [13]. Although, both the PK and PD of inhaled polymyxins are not clearly defined till to date in the human body, however, the overall clinical outcomes mostly based on animal models, have made a scope of reliability on polymyxins nebulization for treating RTI mostly, pneumonia with MDR gram-negative bacteria, during this emergency, in association with less chance of adverse events in critically ill patients. Soon, some reliable clinical studies are required specifically in this field to clearly determine the PK and PD of nebulized polymyxins in the human.

7. CONCLUSION

Polymyxins are the last line treatment option for serious infections with MDR gram-negative bacteria and lack of potential antibiotics in this line, polymyxins should be used

rationally and effectively to obtain the maximum clinical benefits from the therapy. Use of polymyxins nebulization in RTIs is such a way that turn off the IV route and optimizes the overall therapeutic outcomes and reduces direct IV route-associated adverse events during this MDR pathogenic emergency.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors**.**

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CONSENT

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