Original Article

A Randomized Clinical Trial Evaluating the Efficacy of Colistin Loading Dose in Critically Ill Children

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ABSTRACT

Objective: Pharmacokinetic and clinical studies recommend applying loading dose of colistin for the treatment of severe infections in the critically ill adults. Pharmacokinetic studies of colistin in children also highlight the need for a loading dose. However, there are no clinical studies evaluating the effectiveness of colistin loading dose in children. **Methods:** In a randomized trial, children with ventilator-associated pneumonia or central line-associated bloodstream infection (CLABSI) for whom colistin was initiated, were enrolled. Patients were randomized into two groups; loading dose and conventional dose treatment arms. In the conventional treatment arm, colistimethate sodium was initiated with maintenance dose. In the loading dose group, colistimethate sodium was commenced with a loading dose of 150,000 international unit/kg, then on the maintenance dose. Both treatment arms also received meropenem as combination therapy. Primary outcomes were overall efficacy, clinical improvement and microbiological cure. Secondary outcomes were colistin-induced nephrotoxicity and development of resistance. **Findings:** Thirty children completed this study. There was a significantly higher overall efficacy in the group received loading dose (42.9 vs. 6.3%, $P = 0.031$). There weren't any significant differences in the clinical and microbiological endpoints. In the subgroup of children with CLABSI, results illustrated a trend toward (though statistically nonsignificant) better clinical cure for patients receiving loading dose. **Conclusion:** This preliminary study suggests that colistin loading dose might have some benefits in critically ill children, specifically in children with CLABSI. Further trials are required to elucidate colistin best dosing strategy in critically ill children with severe infections.

Keywords: *Children, clinical efficacy, Colistin, loading dose, safety*

Introduction

Colistin, a polymyxin antibiotic, was utilized in practice since 1959 but its therapeutic use was limited in the 1970s due to concerns on drug-induced nephrotoxicity. Increasing rates of infections due to extensively drug resistance (XDR) Gram-negative bacteria along with the limited number of new

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antimicrobial agents being introduced, led to reappraisal of colistin in clinical practice without sufficient pharmacokinetic and pharmacodynamics studies.[1-3] Thus, the best dosing strategy of colistin remains to be elucidated.[4,5]

A leading population pharmacokinetic study of colistin in critically ill adults by Plachouras *et al*., revealed that 2–3 days will take for colistin to reach the desired concentration and was the pioneer study to propose that loading dose would improve initial colistin concentrations.[4,6] Further pharmacokinetic studies in adults also supported the loading dose concept[7,8] while some challenged the concept.[9] In line with pharmacokinetic studies, clinical studies also evaluated the efficacy and safety of loading dose in adults[10-13] with variable results. Despite the limited number of clinical trials in this field and the variable results, consensus and the medication monograph warrants administration of a loading dose of 9 MIU in critically ill adults.[3-5,14]

On the other hand, few pharmacokinetics studies of colistin loading dose are available in the pediatric population. Antachopoulos *et al*. demonstrated that with the current dosing regimen, therapeutic concentration of colistin will not be achieved in pediatric patients.[15] A pharmacokinetic study by Mesini *et al*. demonstrated that after administrating 150,000 I. U/kg loading dose of colistin all pediatric patients achieve the desired area under the curve/minimum inhibitory concentration (AUC/MIC) for pathogens with MIC <2 mg/L and suggested considering loading dose in the pediatric population.[16] However, the study results have been greatly challenged,[17-19] and it should be acknowledged that it still remains uncertain whether the dosage of 150,000 international unit (IU)/kg/day of colistimethate sodium employed by Mesini *et al*. provides adequate exposure for colistin in children. Recently, a study of population pharmacokinetics of intravenous colistin in pediatric patients revealed that current dosage recommendations may be suboptimal for many children.[20] Putting together there is paucity of data on colistin pharmacokinetics and best dosing strategy in children.

To the extent of our knowledge, there are no clinical studies evaluating loading dose of colistin in critically ill children. Hence, the purpose of this study was to evaluate the efficacy and safety of incorporating colistin loading dose in a cohort of critically ill children with nosocomial infections due to XDR Gram-negative bacteria.

Methods

This parallel, randomized clinical trial was accomplished in pediatric intensive care units (PICU) of two referral teaching hospitals affiliated to Tehran and Shahid Beheshti Universities of Medical Sciences, Tehran, Iran, from December 2016 to June 2018. The study protocol was approved by the ethics committee (IR.TUMS.PSRC.REC.1396.2744) and registered in the Iranian Registry of Clinical Trials (IRCT) (IRCT20170614034532N2). Written informed consent was obtained from the Children's guardians.

All critically ill children aged 1 month–18 years old with ventilator-associated pneumonia (VAP) or central line-associated bloodstream infections (CLABSI) that had a positive specimen with polymyxin-only-susceptible (POS) Gram-negative bacteria were included. Exclusion criteria were: (i) patients with previous renal failure (acute or chronic), (ii) previous treatment with colistin in the current admission, (iii) treatment with other antibiotics targeted Gram-negative bacteria except for meropenem, (iv) received colistin for <72 h and/or (v) receiving colistin by inhalation.

Data including demographic and clinical characteristics of patients, results of laboratory tests, cultures and medication history specifically concurrent nephrotoxic drugs were recorded for each patient. Pediatric risk of mortality score III on PICU admission was also calculated.

Participants were randomly assigned (1:1) to the intervention group (loading dose) or to the control arm (conventional dose) by permuted block randomization. In the loading dose group patients received 150,000 IU/kg colistimethate sodium (Forest laboratories; Ireland), based on actual body weight intravenously (IV) as loading dose over 1 h infusion as soon as the diagnosis of VAP or CLABSI had been made. After 12 h, maintenance dose of 150,000 IU/kg/day colistimethate sodium divided every 8 h IV was commenced. In the conventional dose group patients received 150,000 IU/kg/day colistimethate sodium divided every 8 h IV without loading dose. In both treatment groups patients also received meropenem 30 mg/kg/q8 h IV as combination therapy with colistin. Participants were followed 72 h from beginning of colistin therapy for efficacy outcomes.

Primary outcomes were overall efficacy, clinical improvement and microbiological response. Clinical improvement was defined as alleviation in signs such as fever, leukocytosis and for VAP also as improvement of all baseline signs and symptoms associated with pneumonia such as hypoxemia, increased or purulent secretions and respiratory status.

Microbiological response was defined as microbiologically clearance of the isolated causative

organism. Overall efficacy was defined as achieving both clinical and microbiological response. Overall efficacy, clinical improvement and microbiological response were assessed after 72 h after the antimicrobial regimen commencement.

Secondary outcomes were the incidence and severity of acute kidney injury (AKI) and development of resistance to colistin. To explore the probable effect of a loading dose on AKI development, we used the pediatric modification of the RIFLE definition (pRIFLE) criteria [Table 1]. In this regard, serum creatinine (Scr) concentration and estimated creatinine clearance based on Schwartz formula of participants were recorded daily from the 1st day of colistin therapy for 4 days.[21,22] For pRIFLE criteria severity grading, the maximum Scr value achieved in the follow-up was compared with the baseline Scr. The lowest Scr level in the last 3 months before starting colistin was considered as the baseline of Scr level of the patient.[22] Data on concomitant nephrotoxic medications were collected during colistin use. Concomitant nephrotoxins recorded were aminoglycosides, acyclovir, ganciclovir, vancomycin, amphotericin B, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, nonsteroidal anti-inflammatory drugs, intravenous contrast media, loop diuretics, cyclosporine, tacrolimus and vasopressors.

Resistance to colistin was evaluated in children with a second positive organism after 72 h of therapy and was defined if the second MIC was at least twice as much as the first one.[23]

An isolate was defined as POS if it was susceptible to colistin but resistant to antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones.[24] To determine the microbiological sensitivity, clinical and laboratory standards institute guidelines has been used.[25] The sensitivity of specimens to colistin was assessed by E-test and the MIC of ≤2 mg/l was considered sensitive. VAP was defined based on the imaging, clinical and laboratory findings and CLABSI was defined based on the Centers for Disease Control and Prevention definition.[26]

Statistical analysis was done based on SPSS software (Statistical Package for the Social Sciences, version 16, SPSS Inc., Chicago, IL, USA). Results were presented as median (for quantitative variables) or percentage (for qualitative variables). Mann–Whitney U analysis was used for continuous nonparametric varieties. Categorical variables were compared by Chi-square or Fisher's exact test when appropriate. $P < 0.05$ was considered statistically significant.

Table 1: Pediatric RIFLE classification of acute kidney injury

pRIFLE stage	eCCl	Urine output
R=Risk for renal dysfunction	eCCl decreased by 25%	<0.5 mL/kg per hour for 8 h
I=Injury to the kidney	eCCl decreased by 50%	<0.5 mL/kg per hour for 16 h
F=Failure of kidney function	eCCl decreased by 75% or eCCl <35 mL/min per 1.73 m^2	<0.3 mL/kg per hour for 24 h or anuria for 12 h
L=Loss of kidney function	Persistent failure >4 weeks	
E=End-stage renal disease	Persistent failure >3 months	

eCCl=Estimated creatinine clearance

Results

Of 53 children with VAP or CLABSI that had a POS culture, thirty children completed the study (14 patients in the loading dose group and 16 patients in the conventional dose group) [Figure 1]. The clinical characteristics of patients are outlined in Table 2.

Clinical outcome data are depicted in Table 3. As shown in Table 3, there was a statistically significant difference in terms of overall efficacy between the 2 treatment arms. However, no statistically significant difference was noted in clinical improvement and microbiological response between the two treatment groups.

To further explore the effect of underlying disease on outcomes, participants were categorized in the following groups; VAP and CLABSI and the probable effect of loading dose on primary outcomes was assessed in each, separately. In subgroup of children with VAP, there was no statistically difference in clinical

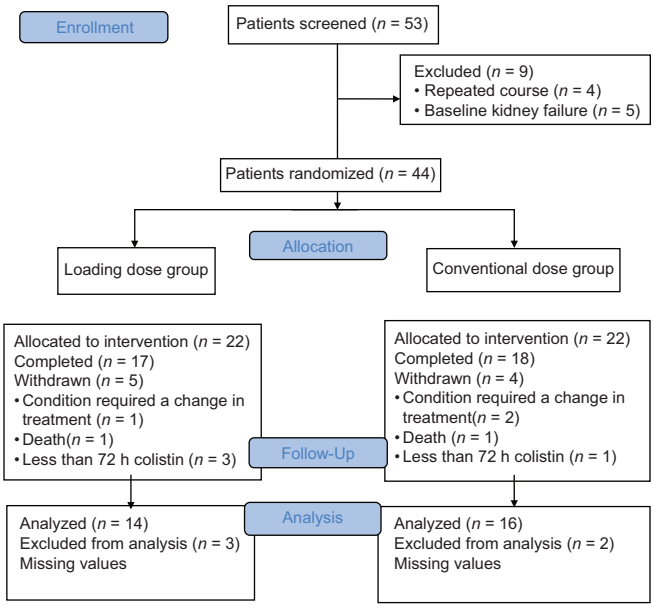

Figure 1: CONSORT flow diagram

Table 2: Clinical characteristics of the studied patients

Characteristics	Loading dose group (*n*=14)	Conventional dose group (*n*=16)	*P*
Age (months) median (range)	7 (1.5-192)	42 (1.5-132)	0.313
Sex (male), *n* (%)	7 (50)	12 (75)	0.156
PRISM III, median (range)	7 (0-37)	10 (5-38)	0.286
Site of infection, *n* (%)			
Ventilator-associated pneumonia	7 (50.0)	8 (50.0)	0.99
Bloodstream infection	7 (50.0)	8 (50.0)	
Underlying diseases			
Congenital heart diseases	4 (28.6)	4 (25)	0.537
Neurological/neuromuscular disorders	4 (28.6)	2 (12.5)	
Malignancy	1 (7.1)	4 (25)	
Gastroenterology	2 (14.3)	2 (12.5)	
Primary immunodeficiency	0	2 (12.5)	
Others (collagen tissue disease, chronic lung disease, trauma)	3 (21.4)	2 (12.5)	
Pathogens, *n* (%)			
Acinetobacter baumannii	5 (27.7)	11 (68.8)	0.205
Klebsiella pneumoniae	6 (42.9)	4 (25)	
Escherichia coli	3 (21.4)	1 (6.3)	
Concomitant nephrotoxic drugs, *n* (%)	12 (85.7)	13 (81.3)	1

PRISM III=Pediatric risk of mortality score

Table 3: Clinical efficacy data

Primary outcomes	Loading dose group (*n*=14)	Conventional dose group (*n*=16)	*P*
Clinical improvement, *n* (%)	10 (71.4)	7 (43.8)	0.127
Microbiological cure, *n* (%)	8 (57.1)	5 (31.3)	0.153
Overall efficacy, *n* (%)	6 (42.9)	1 (6.3)	0.031

improvement and microbiological response between those receiving loading dose and standard treatment ($P = 0.714$ and $P = 0.185$, respectively). In the subgroup of children with CLABSI, results illustrated a trend toward (though statistically nonsignificant) better clinical cure for patients receiving loading dose compared with standard treatment.

In our study, AKI was detected in only two patients based on p-RIFLE criteria. One child in the loading dose group (7.1%) and one in the standard dose group (6.3%); $P = 1$. Both cases were stage R and received nephrotoxic drugs concomitantly with colistin. The time to AKI onset was on day 1 and day 4 of treatment. AKI was successfully reversed by supportive treatment.

Among children with a second positive POS organism after 72 h of treatment, MIC was not increased, thus no cases of resistance to colistin were observed.

Discussion

To our knowledge, the present study is the first randomized clinical trial evaluating clinical effects and safety of colistin loading dose in critically ill children. Results of current study illustrated improved overall efficacy with such a regimen without further jeopardizing renal function.

In adult critically ill patients, data regarding benefits of administrating a loading dose of colistin are derived from pharmacokinetic researches and clinical studies that were mainly observational.[4,5] The idea was first proposed by Plachouras *et al*. and Garonzik *et al*.[6,27] In corroboration with the above pioneer trials, three pharmacokinetic studies applied a loading dose and measured colistin concentration in adult patients.[7-9] Mohamed *et al*. used a loading dose of 6 MU colistin in 10 critically ill adults and noticed average C_{max} of 1.34 mg/l at 8 h after loading dose.[7] Karaiskos *et al*. applied loading dose of 9 MU, and observed average Cmax of 2.65 mg/l after 8 h, a concentration that well exceeded the desired target for bacterial kill.[8] However, Grégoire *et al*. pharmacokinetic study challenged this dosing strategy.[9] The discrepancies observed in plasma concentrations could be attributed to colistin solution preparation, storage, and infusion time.[5]

Several clinical studies performed in adults also evaluated efficacy and safety of loading dose[10-13] with variable results. Dalfino *et al*. trial was the first published study evaluating efficacy of 9 MU loading dose of colistin in critically ill adults, and reported 82% clinical cure and 73% microbiological response. Nephrotoxicity was observed in 17.8% of patients.[10] In a comparative study of 2 matched series by Trifi *et al*., which evaluated both a higher dose and loading dose of colistin, there was a higher rate of clinical cure in

the loading dose colistin group than standard dose group (63 vs. 41.3%, $P = 0.04$) without increasing in the risk for renal toxicity.[11] As mentioned, in the study the two groups also differed in the total daily dose of colistin administered and the observed difference could be attributed to both interventions. Elefritz *et al*. evaluated the effects of colistin loading of 5 mg/kg/colistin base activity (CBA) with a high maintenance dose (7 mg/kg CBA/day) dose in critically ill adults with VAP. The majority of the patients also received inhaled colistin. The study compared outcomes pre- and post-implementation period. The authors did not observe increased clinical cure after implementation of loading dose. There was no difference in time to clinical cure and in-hospital mortality. However, loading dose was not associated with increased incidence of AKI. The authors concluded that loading dose was not a predictor of clinical cure while there is an opportunity to optimized colistin dosing. However, the study was underpowered to detect such an effect.[12] In a cohort study by Katip *et al*., patients received 300-mg CBA as loading dose followed by maintenance dose 150 mg CBA twice daily. Compared with comparator group who only received maintenance dose, improved microbiological clearance was noted and the incidence of nephrotoxicity was similar in the two groups. The authors proposed high loading dose as a safe and effective strategy.[13]

Putting together, although the results of pharmacokinetic, observational and clinical trials are still inconclusive;[5] and the best loading dose and several aspects regarding pharmacokinetic and pharmacodynamics properties of colistin are still debated, most authorities recommend applying loading dose in adult critically ill.[2-4,14]

In the pediatric population, fewer data are available. Antachopoulos *et al*. pharmacokinetic study in 3 patients aged 1.5 months to 14 years who received IV colistin (60,000–225,000 IU/kg/d), only in one of the five courses of colistin treatment (14 years old taking 225,000 IU/kg/d), did serum concentration exceed the 2 mg/l.[15]

The present study was the first clinical trial evaluating colistin loading dose in pediatrics. We did not observe increase microbiological and clinical improvement separately which could be attributed to the small sample size. However, when clinical and microbiological response were assessed together as overall efficacy, improved outcomes with loading dose was observed. Of note, when participants with CLABSIs were analyzed, clinical improvement was nearly significant. This issue could be interpreted as children with CLABSI may benefit more of applying loading dose compared with children with VAP. This suggests the concept that inhaled colistin might be a much more critical determinant of clinical efficacy in VAP patients compared to loading dose; since it generates a high local concentration. This issue needs to be defined in larger clinical trials.

In our study incidence of AKI was similar after administrating loading dose. In line with this finding, currently available data has not illustrated a higher risk of AKI with loading dose.[5]

This study had a number of limitations. First, we had a small sample size. Second, there was a short period of follow-up. However, we wanted to assess successfulness of prescribing a loading dose of colistin in the critical initial hours of infection. If the study was designed to assess clinical efficacy and nephrotoxicity of colistin in critically ill pediatrics, mortality and length of ICU and hospital stay had to be assessed and a longer follow-up was needed, respectively. Further trials with survival analysis and length of hospitalization assessment are suggested. Third we could not assess colistin neurotoxicity including apnea with administration of loading dose.

The present study is the first randomized trial that evaluated the efficacy of a loading dose of colistin in critically ill children. This preliminary study suggested that loading dose might have improved outcomes, especially in patients with CLABSIs. Further clinical trials with larger sample size are needed to shed light on the best dosing strategy of this last-resort antibiotic and to aid in medical decision-making.

Authors' Contribution

Shiva Fatehi selected patients, obtained and interpreted data, done literature research, drafted the manuscript. Hamid Eshaghi designed the study, selected patients, obtained, interpreted data and defined the intellectual content. Meisam Sharifzadeh selected patients, obtained, interpreted data and defined the intellectual content. Bahador Mirrahimi selected patients and obtained data. Mostafa Qorbani carried out statistical analysis. Parin Tanzifi obtained and interpreted data. Toktam Faghihi contributed in concept, defined the intellectual content, designed the study, done literature research, interpreted the data, drafted and revised the manuscript. Kheirollah Gholami defined the intellectual content, contributed in concept, designed and supervised the study.

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Conflicts of interest

There are no conflicts of interest.

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