RESEARCH PAPER

Safety and Efficacy of Intravenous Colistin in Children

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Objective: To observe the safety and efficacy of Colistimethate sodium in children infected with gram-negative bacteria, susceptible only to colistimethate sodium. **Methods:** This prospective observational study done over 2 years observed children who received colistin for >48 h, for renal failure as defined by p-RIFLE criteria. **Results:** Out of 68 children, 52 (76.5%) survived. There were three children with evidence of acute kidney injury and none had neurotoxicity. Serum creatinine significantly decreased at 48 h and at end of treatment, from that at beginning of therapy (*P*=0.007). **Conclusion:** Colistimethate sodium is effective against carbapenem-resistant Gram-negative bacteria, and is safe in children.

Keywords: *Acute kidney injury, Antimicrobial resistance, Colistin.*

Gram-negative bacteria around the world are becoming increasingly resistant to conventional antibiotics including carbapenems [2] this has led to a renewed interest in antibiotics like Colistimethate sodium, which were abandoned in 1980s because of nephrotoxicity and neurotoxicity [3].

Documentation of pediatric usage of colistin has been limited to only few case reports or small retrospective studies [4-7]. We planned this prospective study to observe the safety profile and efficacy of colistimethate sodium for treatment of infections caused by multi drug resistant gram-negative bacteria in children.

METHODS

This prospective descriptive study was conducted from January 1, 2010 to December 31, 2011. The study was approved by hospital Ethical Committee. All children in whom gram-negative bacteria susceptible only to colistimethate sodium were isolated from sterile fluids and/or children who had ventilator associated pneumonia with positive tracheal cultures were studied. All children who received colistimethate sodium for <48 hours were excluded from the study. The dosage of colistimethate sodium was 75,000 to 120,000 IU/kg/d in three divided doses; acute kidney injury (AKI) was defined according to p-RIFLE criteria [2].

Serum creatinine and blood urea were monitored at pre-therapy, 48 hours, 96 hours, and at the end of treatment. Urine output was measured 6 hourly for the first five days of therapy. Cultures were only repeated if clinical cure was not achieved. Data were filled into a proforma by the respective registrar/fellow and the data was analyzed at the end of the study for survival and toxicity of colistimethate sodium. Statistical analysis was done using paired *t*-test and repeated measures of analysis of variance; *P* value <0.05 was considered statistically significant.

RESULTS

A total of 68 patients (47 males) were included in this study. Out of 39 neonates, 18 were preterm and 35 received ventilation. Out of 29 patients aged more than 4 weeks, 25 were ventilated. Median age of patient was 16 days (range 3 d–14y), and mean duration of therapy was 11.6 days. Two patients required more than one course of colistimethate sodium for microbiological clearance and clinical recovery. *Acinetobacter* was the commonest organism isolated (blood 17, trachea 36, CSF 3, central line 1 and peritoneum 1), followed by *Klebsiella* (blood 3, trachea 8, CSF 1 and urine 1), followed by *Pseudomonas* (blood 3, trachea 1), *Yersinia* (blood 1) and *E. coli* (blood 1, trachea 1).

Fifty two (76.5%) patients survived and death in 18 (23.5) was attributed to persistence of sepsis and multi-organ dysfunction. Out of the 16 children who died, five received less than five days of colistimethate sodium.

Three patients (2 preterm neonates) had acute kidney injury (AKI) as per p-RIFLE criteria [2]. All these patients who developed AKI died; one of them was also receiving concomitant nephrotoxic drugs.

Serum creatinine at 48 hours of therapy and at the end of the treatment decreased significantly (*P*=0.007) from baseline. The other biochemical parameters also showed

WHAT THIS STUDY ADDS?

- Colistimethate sodium is safe and efficacious in children having multi drug resistant gram negative sepsis.

improvement on therapy (***Table* I**). No other toxic effects of colistimethate sodium therapy were observed, except for apnea on third and twelfth day of colistimethate sodium therapy in two preterm neonates.

TABLE I BIOCHEMICAL CHARACTERISTICS OF STUDY SUBJECTS.

	Pre-therapy mean(SD)	*Post-therapy mean(SD)*	*P Value*
Serum creatinine (mg/dL)	0.5 (0.2)	0.5 (0.17)	0.145
Blood urea (mg/dL)	36.7 (22.9)	31.6 (19.6)	0.133
Platelets (lakhs/cumm)	1.7 (1.70)	2.9 (1.92)	<0.001
C-reactive protein (mg/L)	33.8 (27.3)	14.7 (22.2)	<0.001

DISCUSSION

In our series of 68 children with multi drug resistant gram-negative sepsis, survival rates use 76% with intravenous colistin therapy; only 3 children developed AKI. Though creatinine estimation is considered a gold marker [9] for renal function estimation, in neonates it is influenced by prematurity and maternal creatinine levels. With a predominant neonatal population, it can be considered as a limitation of our study. Considering the fact that there was only one neonate who was started colistimethate sodium in the first week of life, the effect of maternal creatinin levels would have been negligible.

The survival rate in our study is broadly in agreement with other case series [4,6,7,10] where survival of 75-84% has been reported. Renal toxicity in other studies varied from 0-22% [4,11-13]. Paradoxically, the creatinine values in our study were significantly better after 48 hours and at the end of therapy, probably because of improvement in sepsis. Larger controlled trials are needed to study the safety of colistimethate sodium, particularly in the setting of multi organ dysfunction.

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