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Original Research Article

# Safety Profile of Intravenous Colistimethate Sodium among Critically Ill Neonates with Sepsis in Terms of Serum Creatinine Clearance, Serum Electrolyte Levels and Apnea Incidence

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**Abstract**

There has been increased neonatal mortality and morbidity due to emergence of gram-negative bacteria which is multi-drug resistant (MDR). Neonatal sepsis is the one of the leading causes of neonatal mortality and morbidity in developing and developed countries. Colistin (colistimethate sodium), potent antimicrobial, a cyclopeptide antibiotic of the polymyxin class, has been re-evaluated over the last few decades against certain gram-negative bacteria causing multi drug resistant sepsis. The most common adverse effect of colistin treatment is renal toxicity along with electrolyte imbalance.

**Objectives:** Study was performed to analyze an effect of use of intravenous colistimethate sodium on serum creatinine clearance, serum electrolyte levels and apnea incidence in critically ill neonates with sepsis

**Methods:** Total 62 neonates (28 days) admitted in the hospital with evidence of blood culture positive sepsis and who have received intravenous colistimethate sodium for more than 7 days were included in the study. Serum creatinine levels and serum electrolytes levels were documented before starting colistin, on 7th day of colistin and on discharge. Apnea count was done daily during administration of colistin therapy for 7 days.

**Results**: Most of the study population were of 1 to 7 days (61.3%) followed by 8 to 14 days (16.1%), 15 to 21 days (14.5%) and more than 21 days (8.1%). There was male predominance (59.7%) amongst study population. Most of the babies were preterm (56.5%) followed by term (40.3%) and post-term (3.2%). Pseudomonas (33.9%) was one of the commonest organisms isolated on blood culture followed by Acinetobacter (21%), Candida (19.4%) and Klebsiella (16.1%). There was significant change in potassium and chloride level on 7th day after colistin as compared to pretreatment and discharge level but both values lie in the normal range. No significant difference was observed in serum creatinine and sodium level. Incidence of apnea

was observed significantly in preterm babies (100%) as compared to term (0%) and post term babies (0%). Incidence of apnea was not increased after administering Colistin

**Interpretation And Conclusions**: Intravenous Use of Colistimethate sodium in neonates who are critically ill was not associated with drug related adverse effects like electrolyte imbalance, raised serum creatinine level and increased incidence of apnea episode.

**Keywords:** Neonatal sepsis, colistimethate, creatinine clearance



## Introduction

Sepsis is defined as a systemic inflammatory response syndrome resulting from a proven or suspected.[1] The clinical presentation of neonatal sepsis is non-specific and includes: fever, respiratory distress, impaired or refusal of feeding, lethargy, hypothermia, convulsions, jaundice, absent Moro reflex.[2]

Sepsis presenting within the first 72 hours of life which is called as Early onset sepsis. The neonates may be symptomatic at birth in severe sepsis conditions. Maternal urogenital tract is often a source of infection in early onset sepsis cases.[3] However sepsis presenting after 72 hours of age (Late onset sepsis) is usually community acquired or nosocomial meaning hospital acquired[4]·Emergence of multidrug-resistant (MDR) Gram-negative pathogens, especially Pseudomonas, Acinetobacter and Klebsiella species posed a real challenge for the clinicians and Microbiologists. There are limited discoveries of newer antimicrobials in the recent time[5]· Hence, this study of the clinical application of intravenous Colistimethate sodium (Colistin), a polymyxin class cyclopeptide antibiotic was taken in the awake of limited therapeutic choices. Colistin's surface detergent like action, makes it more effective against the pathogenic organisms especially Gram-negative organisms.[6]

Higher association of toxicities especially nephrotoxicity (20%) was associated with intravenous Colistin, in the previous studies.[7,8] However, less severe and less frequent toxicities were found in recent studies associated with Colistin.[9] We found presence of Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and to a less frequency, staphylococcus aeuroginosa strains in our NICU. Since, they respond well to colistin, we treated these neonates with colistimethate sodium. There is lot to know about safety and efficacy of colistin especially because of simultaneous use of other drugs and coexisting clinical conditions[10]. As efficacy and safety data is still sparse regarding parenteral use of neonates, we decided to conduct this study in order to re-evaluate the effect of intravenous Colistimethate sodium on serum creatinine clearance, electrolytes levels and apnea incidence in critically ill neonates with sepsis.

**Objectives:**

1. To study the effect on serum creatinine clearance in neonates receiving intravenous Colistimethate sodium.
2. To study the effect on serum electrolytes levels in neonates receiving intravenous Colistimethate sodium.
3. To study the incidence of apnea in neonates receiving intravenous Colistimethate sodium.

**Material and Methods of Study**

**Study Type:** Prospective study

**Study Area:** - Neonatal Intensive Care Unit (NICU) in Tertiary care hospital

**Sample Size:** This study was done on 62 patients, though sample size was 60.

**Study period:** 18 months (August 2017 to December 2019)

**Ethics:** Permission was taken from the institutional ethics committee and subjects were enrolled after taking due informed consent from the lawful guardian.

**Eligibility Criteria**:

**Inclusion and Exclusion criteria:**

**Inclusion criteria:** Neonates (Newly born babies up to age of 28 days) admitted in the hospital with evidence of blood culture positive sepsis and who have received intravenous colistimethate sodium for more than 7 days.

**Exclusion criteria:** Neonates diagnosed with congenital renal anomalies will be excluded.

Total 62 neonates (28 days) admitted in the hospital with evidence of blood culture positive sepsis and who have received intravenous Colistimethate sodium for more than 7 days were included in the study. As per the NICU protocol of our institute, Colistin was administered on clinical suspicion of sepsis. Detailed history was taken from the informant of the study subjects regarding the symptoms, maternal and birth details, etc. Clinical examination of all study subjects was conducted, selected clinical parameters like heart rate, respiratory rate, oxygen saturation by pulse oximetry was recorded. Injection Colistin containing Colistimethate sodium containing 10,00,000 IU dissolved in 10 ml distilled water was given at the dose of 50000 to 150000 IU/ kg/ day in 3 ml normal saline and were given 8 hourly infused over 30 min for 7 days. Serum creatinine levels and serum electrolyte levels were documented before starting, on 7$^{th}$ day and after completion of Colistin therapy (on discharge). Apnea [11] count was done daily during administration of Colistin therapy by single observer to avoid bias for 7 days.

**Results:**

Most of the study population were of 1 to 7 days (61.3%) followed by 8 to 14 days (16.1%), 15 to 21 days (14.5%), and more than 21 days (8.1%). **(Table-I)** There was male predominance (59.7%) amongst study population as compared to female (40.3%) and most of the babies were preterm (56.5%) followed by term (40.3%) and post-term (3.2%). **(Table: I)** 56.5% of study population had Lower Segment Caesarian Section as mode of delivery while 35.5% had Normal Vaginal Delivery as mode of delivery. 3.2% population had Vaginal Delivery with Forceps and 4.8% population had Vaginal Delivery with Vacuum **(Table: I)**. Pseudomonas (33.9%) was the commonest organism isolated on blood culture followed by Acinetobacter (21%), Candida (19.4%) and Klebsiella (16.1%). **(Diagram: I)**

There was significant change in potassium and chloride level on 7th day after Colistin as compared to pretreatment and discharge potassium and chloride but still both the values lie in the normal range. No significant difference was observed in serum creatinine and sodium level **(Table: I).** Incidence of apnea is not increased after administering Colistin **(Table: III)**

**Table I: Clinical Profile of The Patients**

| VARIABLE | FREQUENCY | PERCENT |
|---|---|---|
| 1. AGE GROUPS | | |
| 1 to 7 days | 38 | 61.3 |
| 8 to 14 days | 10 | 16.1 |
| 15 to 21 days | 9 | 14.5 |
| More than 21 days | 5 | 8.1 |

| | | |
|---|---|---|
| 2.GENDER | | |
| Female | 25 | 40.3 |
| Male | 37 | 59.7 |
| 3.GESTATION | | |
| Post term | 2 | 3.2 |
| Preterm | 35 | 56.5 |
| Term | 25 | 40.3 |
| 4.MODE OF DELIVERY | | |
| Lower Segment Caesarian Section | 35 | 56.5 |
| Normal Vaginal Delivery | 22 | 35.5 |
| Vaginal Delivery with Forceps | 2 | 3.2 |
| Vaginal Delivery with Vacuum | 3 | 4.8 |

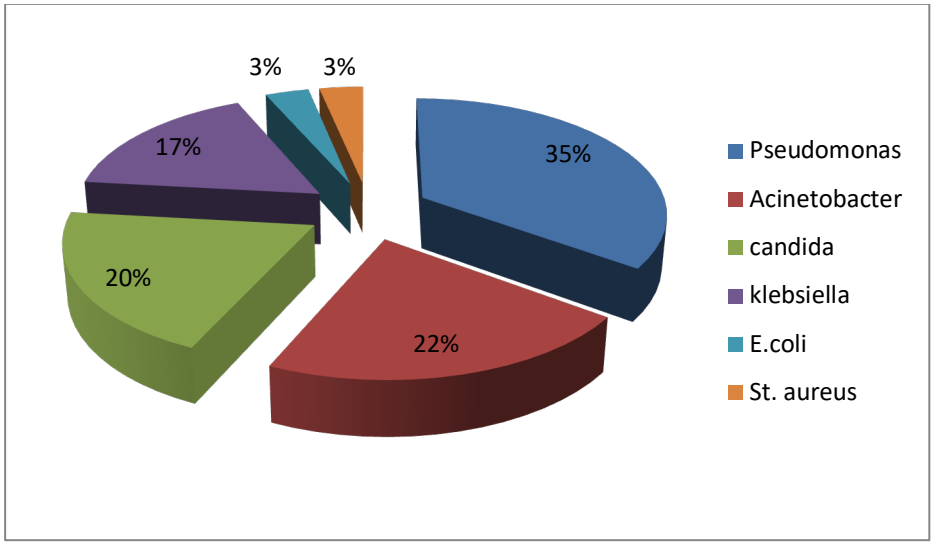


**Diagram I : Blood Culture Growth**

**Table II: Haematological Parameters Before And After Administering Colistin**

| | | Mean | SD | P value |
|---|---|---|---|---|
| Sr Creatinine | Before Colistin | 0.7 | 0.3 | |
| | On 7th Day | 0.6 | 0.2 | 0.109 |
| | On Discharge | 0.7 | 0.2 | 0.200 |
| Sr Sodium | Before Colistin | 138.0 | 5.7 | |
| | On 7th Day | 138.1 | 5.0 | 0.870 |
| | On Discharge | 137.5 | 3.9 | 0.468 |
| Sr Potassium | Before Colistin | 4.8 | 0.7 | |
| | On 7th Day | 4.5 | 0.7 | 0.037 |
| | On Discharge | 4.5 | 0.6 | 0.050 |
| Sr Chloride | Before Colistin | 103.6 | 6.9 | |
| | On 7th Day | 101.8 | 6.7 | 0.019 |
| | On Discharge | 103.1 | 5.7 | 0.594 |

*Unpaired t test

**Table III: Apnea Before And After Administering Colistin**

| Serial no. | Day of Life when Colistin was started | No. of Apnea before Colistin | No. of Apnea after Colistin |
|---|---|---|---|
| Patient no 1 | 3 | 2 | 1 |
| Patient no 2 | 1 | 2 | 2 |
| Patient no 3 | 8 | 2 | 0 |
| Patient no 4 | 3 | 0 | 2 |
| Patient no 5 | 3 | 1 | 0 |
| Patient no 5 | 4 | 3 | 3 |
| Patient no 7 | 25 | 4 | 3 |
| Patient no 8 | 2 | 2 | 2 |
| Patient no 9 | 5 | 2 | 1 |
| Patient no 10 | 5 | 2 | 0 |

*Chi square test, P value- 0.072

## Discussion

Hospital acquired infections or nosocomial infections found to occur in 7% to 33% of the neonates admitted to NICU as per estimation of various studies.[12] Emergence of multidrug-resistant (MDR) Gram-negative pathogens, especially Pseudomonas, Acinetobacter and Klebsiella species posed a real challenge for the clinicians and Microbiologists. There are limited discoveries of newer antimicrobials in the recent time[5]. Hence, this study of the clinical application of intravenous Colistimethate sodium (Colistin), a polymyxin class cyclopeptide antibiotic was taken in the awake of limited therapeutic choices. Colistin's surface detergent like action, makes it more effective against the pathogenic organisms especially Gram-negative organisms.[6]

Higher association of toxicities especially nephrotoxicity (20%) was associated with intravenous Colistin, in the previous studies.[7,8] However, less severe and less frequent toxicities were found in recent studies associated with Colistin.[9] We found presence of Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and to a less frequency, staphylococcus aeuroginosa strains in our NICU. Since, they respond well to colistin, we treated these neonates with colistimethate sodium. There is lot to know about safety and efficacy of colistin especially because of simultaneous use of other drugs and coexisting clinical conditions[10]. Most of the Studies on intravenous use of colistin date back to 1970s. As efficacy and safety data is still sparse regarding parenteral use of neonates, we decided to conduct this study in order to re-evaluate the effect of intravenous Colistimethate sodium on serum creatinine clearance, electrolytes levels and apnea incidence in critically ill neonates with sepsis.

## Age group

In the present study, most of the study population were of 1 to 7 days (61.3%) followed by 8 to 14 days (16.1%), 15 to 21

days (14.5%), and more than 21 days (8.1%).

**Gender**

In the present study, there was male predominance (59.7%) amongst study population as compared to female (40.3%). This finding was similar with Bambala Puthattayil Zakariya et al., (2010) in which 58.3 % were male babies.[13]Also a similar study conducted by Effat Hisamuddin et al., showed male predominance with male patients being 81(55.1%) while female patients 66(44.9%).[14] Krishnakumar Chinnusamy et al., also reported the male predominance (65%) amongst study population.[15] This finding was in agreement with the study conducted by Kumar R et al.66.85% were males.[16]

**Gestation**

In the present study, most of the babies were preterm (56.5%) followed by term (40.3%) and post-term (3.2%). This finding was similar with the study of Kumar R et al., in which 57.54% were preterm babies.[16] Study conducted by Raha BK 2014 consists of majority of preterm babies (71.8%)[17]

**Mode of delivery**

In the present study, 56.5% of study population had Lower Segment Caesarian Section as mode of delivery while 35.5% had Normal Vaginal Delivery as mode of delivery. 3.2% population had Vaginal Delivery with Forceps and 4.8% population had Vaginal Delivery with Vacuum. Similarly in the study conducted by Kumar R et al.LSCS was a mode of delivery in 32%of study population.[16] Ghosh and basu et al., also reported that 47.82% study population had LSCS as a mode of delivery.[18]

**Organism isolated**

In the present study**,** Pseudomonas (33.9%) was the commonest organism isolated on blood culture followed by Acinetobacter (21%), Candida (19.4%) and Klebsiella (16.1%). This finding was similar with study on use of Colistin in a NICU by Eren Çağan et al.(2017) in which almost two-thirds were Gram negative bacteria, the commonest being Acinetobacter sp, Klebsiella sp, Escherichia coli, Pseudomonas sp, and Enterobacter.[19]

**Apnea**

In the present study, apnea incidence is not increased after administering Colistin and apnea was observed significantly in preterm babies (100%) as compared to term babies (0%) and post term babies (0%). Nakwan 2019 did a study on Colistin which shows apnoeic episodes in 12 neonates (3.9 %) ,6 of whom were preterm.[20]

Current study showed apnea incidence of 16.1%. Rajith M. L. et al (2017) conducted a clinical study on apnea in newborn which shows overall apnea incidence of 19 %.[21]

**Serum electrolytes and renal function parameters**

In the present study, there was fall in serum potassium and chloride level after administration of Colistin (On 7$^{th}$ Day) as compared to pretreatment level though both the values lie in the normal range. No significant difference was observed in serum creatinine and serum sodium. However, as per the study conducted by Mehmet SahIpek et al., there was no significant renal impairment found in patients treated with intravenous colistin , However declined levels of serum potassium levels were found in these cases.[8] Retrospective study conducted by Bonny Jasani et al shows that IV Colistimethate was safe and effective in the treatment of neonatal sepsis. No neurotoxicity and nephrotoxicity was seen.[22] ManarAl-lawama et al. conducted a study on Colistin which shows no renal impairment.[23] A study on efficiency and safety of intravenous Colistimethate was carried by Serdar Alan et al in preterm neonates with neonatal

septicemia showed serum electrolyte imbalance (24% ) and acute kidney injury (19%) as a side effect.[24]

**Interpretation and Conclusions**:

In conclusion, Intravenous Use of Colistimethate sodium in neonates who are critically ill was not associated with drug related adverse effects like electrolyte imbalance, raised serum creatinine level and increased incidence of apnea episode. Our results suggest that parenteral colistin treatment is effective and safe and treatment of choice for the treatment of multi drug resistant gram-negative infections in newborns and premature infants with culture proven sepsis. However, more pharmacokinetic and pharmacodynamic studies are required to determine the optimal dose in this age group.

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