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Can we shorten the duration of antibiotics for neonatal sepsis?

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BASED ON ARTICLE

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ABSTRACT

"Antimicrobial stewardship" is the buzz word of today. Shortening the duration of therapy is one of the key components for stewardship. There is growing evidence that we can shorten duration of antibiotic therapy for childhood pneumonia, urinary tract infections, intraabdominal infections, febrile neutropenia and osteomyelitis without compromising efficacy. However neonatal sepsis is generally considered "off limit" for shortening duration of therapy. The standard of care for neonatal sepsis without meningitis is 2 weeks of parenteral therapy. However there have been several trials which have shown shorter treatment of 7-10 days non inferior to 2 weeks of therapy in neonatal sepsis with benefits of cost savings, shortened hospital stay, reduced drug adverse effects/ secondary infections and reduction in antimicrobial resistance. Shorter treatments are even more relevant in today's era of multidrug resistant and extremely drug resistant organisms where drugs are more toxic, expensive and often used off label. At the same time it is uncertain whether shorter treatments will be non-inferior in the current setting of sepsis due to highly drug resistant organisms. This very recent randomized controlled trial attempts to answer this question.

The study was conducted in the neonatal intensive care unit at Burdwan Medical College, Burdwan, West Bengal, India. In this study newborns presenting with culture positive sepsis between January to June 2023 were recruited. Newborns with major congenital anomaly, deep-seated infections including meningitis, multi-organ dysfunction, associated fungal infections/infection by multiple organisms and severe birth asphyxia were excluded. Investigations included complete blood count, CRP, single blood culture (1.5-2 ml of blood) in automated system, lumbar puncture, urine analysis, urine culture and CXR.The first line antibiotics used were ampicillin and amikacin. These babies were randomized on day 9 of illness if they were clinically well as certified by two independent paediatricians into two groups of 10 day and 14 day therapy each. The newborns were followed up for 1 month after stopping antibiotics. Treatment failure defined as development of symptoms and signs of sepsis irrespective of culture results within 30 days after stopping antibiotics was the primary outcome measure. Other secondary outcomes were length of hospital stay and other complications including retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage and hemodynamically significant patent ductus arteriosus. A sample size of 234 babies was envisaged to detect a 4% difference in cure rate between the two groups.

In the mentioned time period, 2471 newborns were admitted; 287 newborns developed culture-positive sepsis, and 53 were excluded [meningitis—15, multi-organ dysfunction and shock—12, severe birth asphyxia—9, fungal co-infection—7, major congenital anomaly—2, infection by multiple organisms—2, left against medical advice—2, refusal of consent—2, osteomyelitis—1, septic arthritis of knee—1] to finally randomize 234 newborns in the study and control groups. The median birth weight and gestational age of the study population were 2.424 kg and 37.3 weeks respectively. There was no significant difference in baseline characteristics between the study groups. Gram-negative organisms were responsible for 61.1% of cases (n =143). Acinetobacter was the most commonly (56, 23.9%) isolated species, followed by Klebsiella (44, 18.8%) and coagulase-negative Staphylococcus (39, 16.7%), followed by E. coli, S. aureus. Enterococcus, Pseudomonas. The clinical and laboratory features and the bacteriological profile of the study and control groups were similar except for total leukocyte count. Treatment failure was similar in the study and control groups (3.8% vs. 1.7%, p=0.40). NO differences were noted in other subgroups preterm (5.7% vs. 2%, p =0.31), term (1.6% vs. 1.5%, p =0.97), Gram-positive (2.2% vs. 2.3%, p= 0.99) and Gram-negative (4.3% vs. 1.4%, p=0.30). Duration of hospital stay was significantly lower in the study group [median 13 days vs. 16 days, $p < 0.001$].

DISCUSSION

"Antimicrobial stewardship" is the buzz word of today. Shortening the duration of therapy is one of the key components for stewardship. There is growing evidence that we can shorten duration of antibiotic therapy for childhood pneumonia, urinary tract infections, intraabdominal infections, febrile neutropenia and osteomyelitis without compromising efficacy. However neonatal sepsis is generally considered "off limit" for shortening duration of therapy. The standard of care for neonatal sepsis without meningitis is 2 weeks of parenteral therapy. However there have been several trials which have shown shorter treatment of 7-10 days non inferior to 2 weeks of therapy in neonatal sepsis with benefits of cost savings, shortened hospital stay, reduced drug adverse effects/ secondary infections and reduction in antimicrobial resistance. Shorter treatments are even more relevant in today's era of multidrug resistant and extremely drug resistant organisms where drugs are more toxic, expensive and often used off label. At the same time it is uncertain whether shorter treatments will be non-inferior in the current setting of sepsis due to highly drug resistant organisms. This very recent randomized controlled trial attempts to answer this question.

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were length of hospital stay and other complications including retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage and hemodynamically significant patent ductus arteriosus. A sample size of 234 babies was envisaged to detect a 4% difference in cure rate between the two groups.

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