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ORIGINAL ARTICLE

TEN DAYS VERSUS FOURTEEN DAYS ANTIBIOTIC THERAPY IN CULTURE PROVEN NEONATAL SEPSIS: SINGLE CENTER EGYPTIAN EXPERIENCE

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ABSTRACT

Aim: To compare the efficacy of a 10 days course versus the conventional 14 days course of antibiotic therapy in neonatal sepsis proven by blood culture.

Methods: The study was done in the neonatal intensive care unit (NICU) in 30 neonates with culture positive neonatal sepsis. They were subdivided into 2 groups: 15 cases for 10 days antibiotic therapy and 15 cases for 14 days antibiotic therapy. C-reactive protein (CRP) and blood culture were repeated at 48 hours after stopping antibiotic therapy in all the babies in both groups. All babies were followed up on a weekly basis for a period of 4 weeks.

Results: No statistically significant difference was noted in both the groups regarding the clinical recovery, but the mean duration of hospital stay was statistically significant (p value=0.0001). After 4 weeks follow-up, there was no statistically significant relapse rate with 2 relapses in neonates who received 10 days antibiotics and 1 relapse in the 14-day antibiotic group (p value=0.54).

Conclusion: Ten days antibiotic therapy is effective as 14 days antibiotic therapy in culture proven neonatal sepsis.

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KEYWORDS

neonatal sepsis, antibiotics, culture, Egypt

Introduction

In Egypt, neonatal mortality rate due to neonatal sepsis is 20/1000 according to Egypt Demographic and Health Survey (EDHS).[1] Early diagnosis and treatment of the newborn infant with suspected sepsis are essential to prevent severe and life-threatening complications. It is mandatory to avoid unnecessary use of antibiotics in non-infected infants. Thus, rapid diagnostic test(s) that differentiate infected from non-infected infants, particularly in the early newborn period, have the potential to make a significant impact on neonatal care.[2] Optimal duration of empiric antimicrobial use decreases the development of antimicrobial resistance, prevents unwanted changes in flora found in the neonatal intensive care unit (NICU) and minimizes unnecessary expenses for infants who have negative blood cultures.[3] Prolonged duration of initial empirical antibiotic therapy is associated with an increased risk of necrotizing enterocolitis and death in (extremely low birth weight) ELBW infants.[4] The inadvertent use of broad-spectrum antibiotics has led to the emergence of multi-drug resistant (MDR) gram-negative bacteria and *klebsiella spp.* are of significant importance in this regards.[5,6] This study was designed to compare the efficacy of a 10 days course of antibiotic therapy versus the conventional 14 days course of antibiotic therapy, in neonatal sepsis proven by blood culture.

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Methods & Materials

This study was done on 30 neonates with gestational age (GA) 36 weeks or more and birth weight 2 kg or more who had blood culture positive neonatal sepsis in NICU of Alhrar hospital - Al-Sharkia governorate, Egypt. An informed consent was obtained from the parents of all babies enrolled and the study was cleared by the hospital ethics committee. Neonates were then subdivided randomly into 2 groups of 15 patients each where the study group received 10-days antibiotic therapy and control group received 14-days antibiotic therapy. Babies with birth asphyxia, congenital malformations and those with evidence of deep-seated foci of infections, such as meningitis, osteomyelitis, septic arthritis were excluded. All groups were subjected to a full detailed history, thorough clinical examination & evaluation for signs of sepsis, and laboratory screening of sepsis including complete blood count (CBC), C-reactive protein (CRP) and blood culture. Clinically sepsis was suspected if the neonate had features such as brady/tachycardia, feeding intolerance, hypoglycemia, hypothermia, fever, respiratory distress, lethargy, poor cry, poor perfusion or metabolic acidosis Leucocytosis was defined if white blood cell (WBC) count was >25,000 cells/cumm, leucopenia was defined if WBC count was <5000 cells/cumm, thrombocytopenia was defined if platelet count was <100,000 cells/cumm. The immature-to-total (I/T) neutrophil ratio >0.2 was considered as positive sepsis screen. C-reactive protein (CRP) >5 mg/dl was considered as positive. CRP estimation was done by a semiquantitative latex agglutination method. Patients were determined to have neonatal sepsis if there they had a positive bacterial growth on blood culture with clinical features suggestive of sepsis or any 2 hematological abnormalities such as

leucopenia/leucocytosis, positive I/T neutrophil ration, thrombocytopenia, or a positive CRP along with clinical features suggestive of sepsis. Premature rupture of membranes (PROM) was defined as if the membranes ruptured at least 18 hours prior to delivery of the child. Premature delivery was defined as babies born before gestational age of 37 weeks. Pre-eclampsia in the mother was defined if she had new-onset hypertension (blood pressure >140/90 mm Hg) plus new unexplained proteinuria (>300 mg/24 hours or urine protein/

Table 1. Baseline characteristics of patients in both the groups

Baselines characteristics	Neonates that received 10 days antibiotic course (n=15) (%)	Neonates that received 14 days antibiotic course (n=15) (%)
Gestational age (weeks) (Mean±SD)	34 ± 4	35 ± 6
Birth weight (gm) (Mean±SD)	1950 ± 970	2050.6 ± 420
Type of delivery Vaginal LSCS	 12 (80) 3 (20)	 13 (86.6) 2 (13.4)
PROM	5 (33.3)	4 (26.6)
Onset of sepsis Early <3 days Late >3 days	 6 (60) 9 (40)	 10 (66) 5 (34)
Leucocytosis	2 (13.3)	2 (13.3)
Leucopenia	5 (33.3)	3 (20)
Thrombocytopenia	5 (33.3)	6 (40)
I/T ratio >0.2	8 (53.3)	8 (53.3)
Positive CRP	15 (100)	13 (86.6)
Organisms grown on blood culture - *Klebsiella pneumoniae* - CONS -*Acinetobacter baumanii* - Others (MRSA, *Enterococci spp, Pseudomonas aeruginosa, Group B streptococci*)	 7 (46.6) 4 (26.6) 3 (20) 2 (13.3)	 7 (46.6) 3 (20) 3 (20) 1 (10)
Antibiotics	Ampicillin + Amikacin	Ampicillin + Amikacin

Note: PROM: premature rupture of membranes, LSCS: Lower Segment Caesarean Section, CRP: C-Reactive Protein, I/T ratio: Immature/Total neutrophil ratio, MRSA: Methicillin resistant Staphylococcus aureus, CONS: Coagulase negative staphylococcus aureus.

Table 2. Outcome of patients post antibiotic therapy

Outcome	Neonates that received 10 days antibiotic course (n=15) (%)	Neonates that received 14 days antibiotic course (n=15) (%)	P value
Mean duration of hospital stay (days)	13.03 ± 1.7 days	17.5 ± 2.2 days	0.0001
CRP negative	13 (86.7%)	14 (93.3%)	>0.05
Leucopenia	1	0	
Leucocytosis	0	0	
I/T ratio >0.2	8 (53.3%)	8 (53.3%)	>0.05
Blood culture negative	15 (100%)	15 (100%)	
Clinical outcome - Recovered - Recurrent of sepsis	 13 2	 14 1	0.54

creatinine ratio ≥0.3) after 20 weeks gestation. If the baby had clinically remitted and was CRP negative, CRP and blood culture were repeated at 48 hours after stopping antibiotic therapy in all the babies in both groups. All babies were followed up on a weekly basis for a period of 4 weeks.

Statistical Analysis

Descriptive and analytical statistics were performed on IBM-compatible computer by using SPSS (statistical package for social science). Continuous data were presented as mean ± standard deviation (mean ± SD), categorical data were presented in the form of numbers and percentages. The significant difference between means was determined by student-t-test. Inter-group comparison of categorical data was performed by using chi square test (X2) value. P values <0.05 were considered significant.[7]

Results

Baseline characteristics such as gestational age, birth weight, type of delivery, premature rupture of membrane (PROM) and onset of sepsis as well as sepsis screen parameters and organisms grown on blood culture were similar in both the groups (Table 1). Risk factors for sepsis included maternal urinary tract infection (UTI) in 4 (15%), PROM in 9 (30%), maternal fever in 7 (23.3%), pre-eclampsia in 3 (10%), meconium-stained amniotic fluid (MSAF) in 3 (10%), infant of diabetic mother 3 (10%) and prematurity in 8 (24%). More than 1 risk factor was present in 3 (10%). The antibiotics given in both the groups are depicted in Table 1.

Our study revealed that there is no statistical significant difference between the two groups as regard clinical recovery, but the mean duration of hospital stay was statistically significant (P value=0.0001), and revealed also that there's no significant difference between the two groups regarding WBC, I/T ratio & CRP after treatment (Table 2). Though 2 babies had CRP positive at the end of 10 days of antibiotics in the 10-day antibiotic group and 1 baby had CRP positive at the end in the 14-day antibiotic group, all the neonates were asymptomatic at the end of therapy. However, these babies with positive CRP had a relapse within 4 weeks.

Discussion

Current standard textbooks recommend 14-day antibiotic therapy for culture-proven neonatal sepsis.[8,9,10] The rationale and safety of this has, however, never been scientifically evaluated. Recent reports suggest that shorter courses of antibiotic therapy may be as effective as the conventionally recommended longer therapy[11,12,13] which was also seen in our study where 10 days of antibiotic therapy was as effective as 14 days with a relapse rate being similar in both the groups.

Of the 15 babies who received 10 days of antibiotics, only 2 (15.3%) had CRP positive on day 10 but were asymptomatic. Similarly, 1 patient in the 14 days antibiotic group was CRP positive at the end of therapy but was clinically asymptomatic. In a similar study by Ehls et al[14], infants with CRP levels of 10 mg/L or greater were considered likely to be infected and randomized to two study groups. In 38 of 39 neonates, CRP was determined daily, and antibiotic therapy was discontinued at a mean of 3.7 days as soon as CRP returned to less than 10 mg/L. No patient in this group had a relapse. Forty-three neonates with likely infection were treated for at least 5 days, out of which 2 babies had a relapse within 4 weeks suggesting that CRP could be a parameter to determine the course of antibiotics. In the study by Jaswal et al[15], out of 50 cases (42% culture positive) of suspected neonatal sepsis, 48% were still CRP positive on day 7 of antibiotic therapy needing a longer duration of antibiotic in these patients. However, in the remaining antibiotics could be stopped earlier once the CRP became negative. In a study by Philip et al[16], 8 out of 10 cases of group B streptococcal infection became CRP negative by day 8 of therapy. Thus, CRP may be a good marker to decide on the duration of antibiotics. The babies who relapsed in our study had a positive CRP at the end of the predetermined course of antibiotics. Similar observations have been made by others[17,18] whereby CRP may be a better marker to decide end of antibiotic therapy[14,15].

The treatment failure rate in the 10-day treatment group was comparable with that in the 14-day treatment group, even when the criteria used for treatment failure were stricter than those used by other authors[13,14,19]. The secondary outcome variable in the index study was the mean duration of stay in the hospital. This was significantly shorter in the study group compared with the control group. This would imply lesser cost and also a lesser risk of nosocomial sepsis that is likely with a longer hospital stay. Thus, we documented that 10-day antibiotic therapy was as effective as 14-day therapy in culture-proven neonatal sepsis if the neonate was in clinical remission and CRP negative on day 10 of appropriate antibiotic therapy.

However, the study has some limitations. First, the results of our study are valid for the specified group of neonates studied namely those with gestational age (GA) ≥36 weeks and birth weight >2 kg. Second, we used a semiquantitative latex agglutination method for the estimation of CRP. Ideally, a quantitative method such as nephelometry or radioimmunoassay should have been used. Third, the sample size in the study was small. However, the results of the present study could form a basis for a larger multicentric trial.

In conclusion, we found that ten days antibiotic therapy is effective as fourteen days antibiotic therapy in culture proven neonatal sepsis, with fewer side effects of prolonged duration of antibiotic therapy and prolonged duration of hospital stay. CRP may be used as a marker to decide the duration of antibiotics.

Compliance with Ethical Standards

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Conflict of Interest: None

References :

1. El-Zanaty F, Way A. Egypt demographic and health survey (2005). Cairo, Egypt: Ministry of Health and Population. National Population Council, El-Zanaty and associates, and ORC Macro. 2006; 10: 109-118.
2. Hodge D, Puntis JWL. Diagnosis, preventing and management of catheter related bloodstream infection during long-term parenteral nutrition. Arch Dis Child Fetal

Neonatal J. 2004; 87: 21-24.

3. Nancy M. Bennett, Michael C. Thigpen, Cynthia G. Whitney, et al. Bacterial Meningitis in the United States, 1998-2007. N Engl J Med. 2011; 364: 2016-2025.
4. Cotton MH. Adult necrotizing enterocolitis. Turk J Pediatr. 2010; 52: 464-470.
5. Koksal N, Hacimustafaoglu M, Bagci S, Celebi S. Meropenem in neonatal severe infections due to multiresistant gram-negative bacteria. Indian J Pediatr 2001; 68: 15-19.
6. Roilides E, Kyriakides G, Kadiltsoglou I, Farmaki E, Venzon D, Katsaveli A, Kremenopoulos G, et al. Septicemia due to multi resistant Klebsiella pneumoniae in a neonatal unit: a case-control study. Am J Perinat. 2000; 17: 35-39.
7. Kirkwood BR, Sterne JAC. Essential medical statistics, 2nd ed. Oxford: Blackwell scientific 2003.
8. Guerina N. Bacterial and fungal infection. In: Cloherty JP, Stark AR (eds). Manual of Neonatal care. 4th edn. Philadelphia. Lippincott Raven Publishers. 1997:271-300.
9. Freij BJ, Mc Cracken GH. Acute infections. In: Avery GB, Fletcher MA, Mc Donald MG (eds). Avery's Neonatology. 4th edn. Philadelphia. JB Lippincott Company. 1994:1082-1116.
10. Haque KN. Infection and immunity in newborn. In: McIntosh HP, Smyth R (eds). Forfar and Arneil's Textbook of Pediatrics. 6th edn. Edinburg. Churchill Livingstone. 2003:336-353.
11. Viladrich PF, Pallares R, Ariza J, Rufi G, Gudiol F. Four days of penicillin therapy for meningococcal meningitis. Arch Intern Med. 1986; 146: 2380-2382.
12. Lin TY, Chrone SF, Nelson JD. Seven days of ceftriaxone therapy is as effective as ten days treatment for bacterial meningitis. JAMA. 1985; 253: 3559- 3563.
13. Engle WD, Gregor L. Neonatal pneumonia: comparison of 4 versus 7 days of antibiotic therapy in term and near-term infants. J Perinatol. 2000; 20: 421-426.
14. Ehls S, Gering B, Bartmann P, Högel J, Pohlandt F. CRP is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 1997; 99: 216-221.
15. Jaswal RS, Kaushal RK, Goel A, Pathania K. Role of CRP in deciding duration of antibiotic exposure in neonatal sepsis. Indian Pediatr 2003; 40: 880-883.
16. Philip AGS. Response of C-reactive protein in neonatal group B streptococcal infection. Pediatr Infect Dis J 1985; 4:145-148.
17. Ewerbeck H, Kunzer W, Uhlig T. Serum CRP in early diagnosis of bacterial infection in premature infants. Acta Pediatr Hung 1984; 25: 291-297.
18. Seibert K, Yu VY, Doery JC, Embury D. The value of CRP measurement in the diagnosis of neonatal infection. J Pediatr 1990; 26: 267-270.
19. Bomela HN, Ballot DE, Cory BJ, et al. Use of CRP to guide duration of antibiotic therapy in suspected early neonatal sepsis. Pediatr Infect Dis J 2000;19: 531-535.