Original Paper

Short Course versus Standard Course Antibiotic Treatment for Neonatal Sepsis

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Abstract

Introduction: Neonatal sepsis remains an important cause of morbidity and mortality and often requires prompt empiric treatment. However, only a minority of babies who receive antibiotics for suspected sepsis have an infection. Antimicrobial exposure in infancy has important short-term and long-term consequences. There is no consensus regarding empirical antimicrobial regimens.

Objective: To compare efficacy and benefits of short course (5 days) over the standard course (7 days) antibiotic treatment for neonatal sepsis.

Materials and Methods: The study was a randomized controlled trial done in the neonatal ward in a tertiary level hospital comprising total 100 term neonates equally divided in to two groups by randomization where Group-I (5 days antibiotic therapy) was compared against Group-II (7 days antibiotic therapy) in clinical recovery, hospital stay, morbidity such as seizure, developmental delay etc and mortality.

Results: The study results showed that both the Group-I and Group-II were comparable in baseline clinical data and predisposing factors; however, there was no significant difference between the two groups in clinical features e.g. hypotonia (24% vs 26%, p>0.05), poor primitive reflexes (46% vs 52%, p>0.05), temperature instability (34% vs 28%, p>0.05), feeding intolerance (16% vs 14%, p>0.05), apnea / respiratory distress (28% vs 34%, p>0.05) and in clinical outcome e.g. hospital stay (5.24±0.78 vs 7.86±0.42, p>0.05), recovery (86% vs 90%, p>0.05), death (14% vs 10%, p>0.05), seizure disorder (8% vs 6%, p>0.05) and developmental delay (6% vs 4%, p>0.05).

Conclusion: This study showed that there was no significant difference between the study groups in clinical outcome, however, short course antibiotic (5 days) is equally effective but economically more beneficial to standard course antibiotic (7 days) therapy for neonatal sepsis.

Key-words: Neonatal Sepsis, Short Course, Standard Course, Antibiotic Treatment.

Introduction

Neonates are particularly vulnerable to acquire sepsis and neonatal sepsis remains an important cause of morbidity and mortality and necessitates prompt diagnosis and treatment[1]. Neonatal sepsis is the third major cause of neonatal death, only next to prematurity and perinatal asphyxia[2]. Of all neonatal deaths in the developing countries, nearly one third are attributable to sepsis[3]. Neonates are prone to develop sepsis due to immaturity, low birth weight, multiple gestation, premature rupture of membrane (PROM), unsterile delivery practices, metabolic diseases, prolonged hospital stay, NICU admission etc[4,5]. Incidence of Neonatal sepsis is 1-8 per 1000 live births and as high as 13-27 per 1000 for neonates weighing < 1500 gm. The mortality rate of neonatal sepsis is high[6] (13-25%) and higher rates are seen with premature neonates and those with early fulminant disease[7,8]. The salient clinical features include systemic signs of infection such as fever, hypothermia, hypotonia, poor primitive reflexes, tachycardia, failure to thrive, lethargy, irritability, listlessness as well as isolation of a bacterial pathogen from the bloodstream[9-12]; however, in a substantial number of cases signs and symptoms are nonspecific at presentation[13].

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Very low birth weight neonates are especially vulnerable to neonatal sepsis and often tend to develop severe complications, leading to a fatal outcome[14,15]. Therefore, early diagnosis and implementation of appropriate antibiotic therapy play a crucial role in improving the survival rate of neonates with sepsis[16,17]. The "gold standard" for a diagnosis of the systemic bacterial or fungal infection is the isolation of pathogens from peripheral blood[18]. Unfortunately, the sensitivity of this method is low and thus, a diagnosis of sepsis cannot be excluded even when these results are negative[19]. Neonatal sepsis often lacks specific signs and laboratory investigations lack negative predictive value to confidently refute the presence of infection[20]. So, antimicrobial therapy remains the mainstay for the treatment of neonatal sepsis[21]. Despite this, there is insufficient evidence-based guidelines regarding the optimal duration of antibiotic therapy against neonatal sepsis[22,23]. However, most clinical textbooks and literatures suggest that standard antimicrobial therapy should be of 7-14 days for culture positive or clinically probable neonatal sepsis[24,25]. Prolonged antibiotic use may endanger emergence of bacterial resistance, alteration of microbiome, risk for secondary infections and prolonged hospital stay[26,27].

Recently, several studies have shown that shorter duration of antibiotic therapy against neonatal sepsis may be as effective as conventional longer duration of antibiotic use for septicemia in the newborns[1]. However, very few studies conducting short course versus traditionally accepted longer duration of antibiotic treatment for neonatal sepsis are available. We conducted this randomized controlled trial with the objective of comparing the efficacy of 5 dayss versus 7 dayss antibiotic therapy for neonatal sepsis.

Materials and Methods

This study was a randomized controlled trial conducted in the Neonatal ward of the Sher-e-Bangla Medical College, Barisal from 01 January 2017 to 30 June 2017. Total 100 term neonates diagnosed with neonatal sepsis, were included in this study; these 100 neonates were equally divided into two groups by randomization, Group-I (5 days antibiotic therapy) and Group-II (7 days antibiotic therapy). Neonates diagnosed as prematurity, low birth weight, perinatal asphyxia, congenital anomaly, chromosomal disorders were excluded from the study. Sepsis was defined as the presence of at least two clinical and two laboratory criteria or as a result of suspected or proven infection (positive blood culture). The clinical criteria are (1) body temperature instability; (2) cardiovascular instability; (3) presence of the skin and subcutaneous lesions such as petechial rash or sclerema; (4) apnea or increased oxygen requirement, requirement for ventilation support; (5) feeding intolerance or abdominal distension and (6) irritability, lethargy, or hypotonia. The laboratory criteria were (1) a white blood cell (WBC) count of <4 or >20 × 109 cells/L; (2) an immature to total neutrophil ratio (I/T) of >0.2; (3) a platelet count of <100 × 109/L; (4) C-reactive protein (CRP) levels of >10 mg/L; (5) blood glucose values of >180 mg/dL or hypoglycemia (<40 mg/dL) confirmed at least 2 times.

Neonatal sepsis may be classified according to the time of onset as either early onset neonatal sepsis or late onset neonatal sepsis. Early onset neonatal sepsis is defined as infection occurs in neonates less than 3 days of life and late onset neonatal sepsis is defined as infection occurs in neonates more than 3 days of life. The distinction has clinical relevance, as the early onset variant is primarily due to bacteria acquired before and during delivery or late onset sepsis is due to bacteria acquired after delivery (health acquired or environmental sources).

Results

The baseline clinical data were comparable between the two groups as shown in Table-I.

Table-I: Baseline clinical data between Group-I and Group-II

Clinical data	Group-I	Group-II	P value
Birth weight (gm)	2768±72	2842± 84	>0.05
Gestational age (wk)	37.28±0.82	37.74±0.96	>0.05
Male/female ratio (n,%)	28/22 (56%/44%)	26/24 (52%/48%)	>0.05
Apgar score	8.2±1.8	8.8±2.4	>0.05
Inborn/out born (n, %)	27/23 (54%/46%)	28/22 (56%/44%)	>0.05
Mode of delivery, (cesarean/NVD)	32/18 (64%/36%)	34/16 (68%/32%)	>0.05

Various predisposing factors responsible for neonatal sepsis were evaluated between the two study groups and the results were also comparable as shown in Table-II.

Table-II: Predisposing factors responsible for neonatal sepsis between Group-I and Group-II

Predisposing factor (n, %)	Group-I	Group-II	P value
Premature rupture of membrane (PROM)	06 (12%)	07 (14%)	>0.05
Maternal peripartum fever (≥38^{0}C/100.4^{0}F)	03 (06%)	02 (04%)	>0.05
Meconium stained or foul smelling amniotic fluid	04 (08%)	05 (10%)	>0.05
Multiple gestation	04 (08%)	02 (04%)	>0.05
Unsterile delivery practice	03 (06%)	04 (08%)	>0.05

Clinical features were also comparable between the two study groups as shown in Table-III.

Table-III: Clinical features found in neonatal sepsis in Group-I and Group-II

Clinical feature (n, %)	Group-I	Group-II	P value
Hypotonia	12 (24%)	13 (26%)	>0.05
Poor primitive reflexes	23 (46%)	26 (52%)	>0.05
Temperature instability (fever/hypothermia)	17 (34%)	14 (28%)	>0.05
Abdominal distention	11 (22%)	13 (26%)	>0.05
Feeding intolerance	08 (16%)	07 (14%)	>0.05
Apnea / respiratory distress	14 (28%)	17 (34%)	>0.05
Poor peripheral perfusion	05 (10%)	04 (08%)	>0.05

The study groups were also evaluated by various laboratory investigations and the results were also shown in Table-IV.

Table-IV: Laboratory results of various investigations in Group-I and Group-II

Investigation results	Group-I	Group-II	P value
C reactive protein (CRP) (+ve)	41 (82%)	44 (88%)	>0.05
Thrombocytopenia	08 (16%)	05 (10%)	>0.05
Abnormal WBC count (leukopenia/ leukocytosis)	13 (26%)	12 (24%)	>0.05
Immature to total neutrophil ratio (I/T ratio >0.2)	04 (08%)	05 (10%)	>0.05
Anemia (hemoglobin <13 gm/L)	14 (28%)	11 (22%)	>0.05
Hypoglycemia	10 (20%)	09 (18%)	>0.05
Hyperbilirubinemia	07 (14%)	06 (12%)	>0.05
Culture positive sepsis	05 (10%)	04 (08%)	>0.05

Clinical outcome e.g. hospital stay, rate of recovery, death, morbidity e.g. seizure disorder, developmental delay were evaluated between the study groups and results were shown in Table-V.

Table-V: Clinical outcome of Group-I and Group-II

Clinical outcome	Group-I	Group-II	P value
Hospital stay (days)	5.24 ± 0.78	7.86 ± 0.42	>0.05
Recovered (n, %)	43 (86%)	45 (90%)	>0.05
Death (n, %)	07 (14%)	05 (10%)	>0.05
Seizure disorder (n, %)	04 (08%)	03 (06%)	>0.05
Developmental delay (n, %)	03 (06%)	02 (04%)	>0.05

Discussion

Neonatal sepsis is one of the major causes of neonatal mortality[1]. Empirical use of antibiotics is often required to treat infections in neonates to prevent morbidity and mortality, because neonatal sepsis often lacks specific sign and symptoms and culture positive proof[2]. Excessive antibiotic use has been associated with altered bacterial colonization and may result in antibiotic resistance, fungemia, necrotizing enterocolitis (NEC) and mortality. So, rational use of antibiotics especially in the setting of culture-negative neonatal sepsis is very important[3]. Optimal duration of parenteral antibiotics for treating neonatal sepsis ranges from 7-14 days[4]. We compared the efficacy of 5 dayss versus 7 dayss duration of intravenous antibiotics for neonatal sepsis in this study. The baseline clinical data e.g. birth weight, gestational age, male/female ratio and mode of delivery were comparable between the two groups, (p value>0.05). Similarly, the predisposing factors for neonatal sepsis e.g. PROM, peripartum maternal fever, meconium stained or foul smelling liqour amnii, multiple gestation and unsterile delivery practices were also comparable between the two study groups, (p value >0.05) which were similar to other previous study done by Rohatgi et al[3] and lean et al[4].

The clinical features e.g. hypotonia (24% vs 26%, p>0.05), poor primitive reflexes (46% vs 52%, p>0.05), temperature instability (34% vs 28%, p>0.05), feeding intolerance (16% vs 14%, p>0.05), apnea/respiratory distress (28% vs 34%, p>0.05) were also comparable between the study groups. These findings are also similar to these studies done by Machado et al[8], Cuenca et al[10] and Gerber et al[12]. The investigation results such as CRP (82% vs 88%, p>0.05), thrombocytopenia (16% vs 10%, p>0.05), immature to total leucocyte ratio (I/T ratio >0.2) (8% vs 10%, p>0.05), hypoglycemia (20% vs 18%, p>0.05), hyperbilirubinemia (14% vs 12%, p>0.05), culture positive sepsis (10% vs 8%, p>0.05) were also comparable between Group-I and Group-II. These findings are consistent with the previous studies conducted by Bowen et al[1] and Lean et al[4] The outcome measures were hospital stay (days) (5.24±0.78 vs 7.86±0.42, p>0.05), recovery (86% vs 90%, p>0.05), death (14% vs 10%, p>0.05), seizure disorder (8% vs 6%, p>0.05) and developmental delay (6% vs 4%, p>0.05), also comparable between the Group-I and Group-II. Similar results were found by Shah et al[7], Machado et al[8] and Camacho-Gonzalez et al[13]. However these findings contradict with other studies done by Rohatgi et al[3] and Polin et al[15], where significant difference was found in clinical outcome e.g. hospital stay, recovery rate, morbidity and mortality.

Conclusion

Neonatal sepsis is one of the leading causes of neonatal mortality and morbidity. Optimal use of suitable and effective antibiotics is a must to treat infections in the newborn. Prolonged use of antibiotics often leads to resistance to antimicrobial therapy, longer hospital stay, more economic burden; that is why, research is

going on whether shorter duration of antibiotics is effective to treat neonatal septicemia. In this study, we compared the efficacy and benefits of short course antibiotic (5 days) with conventional course (7 days); though there was no significant difference in death, recovery, seizure disorder and developmental delay but hospital stay was shorter in short course antibiotic than the conventional course. Further studies are needed in this regard to validate the results.

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