Original Article

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Comparison of Short Course of Antibiotic Therapy versus 7-Day Course in Preterm Infants with Probable Sepsis without Meningitis

Rajesh Bansal[1], Ashok K Agarwal[1], Sanjata R Chaudhary[2], Mahender Sharma[3]

[1]Professor, Department of Pediatrics, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India, [2]Professor and Head, Department of Pediatrics, Rohilkhand Medical College, Bareilly, Uttar Pradesh, India, [3]Statistician cum Lecturer, Department of Community Medicine, Rohilkhand Medical College & Hospital, Bareilly, Uttar Pradesh, India

Abstract

Introduction: Neonatal sepsis is a common cause of neonatal morbidity and mortality. The clinical presentation is very non-specific and based on clinical suspicion; empirical antibiotic therapy is usually initiated after taking blood cultures.

Purpose: This study was conducted to assess whether stopping antimicrobials earlier amounts to higher treatment failure compared to conventional 7 days therapy in preterm babies with probable sepsis.

Methods: It was an open-labeled, controlled, prospective, randomized trial conducted in a tertiary care teaching hospital in India. Pre-term babies >30 weeks gestation and weighing >1000 g with probable sepsis (clinical signs of sepsis and C-reactive protein >10 mg/L) were included. Randomization was done after 48-96 h of enrollment and the criteria were resolution of clinical signs of sepsis; sterile blood culture reports and normal cerebrospinal fluid analysis. Eligible babies were randomly allocated in a 1:1 ratio into two groups. In the intervention group, antibiotics were stopped after the 48 h culture was reported sterile. In the control group, antibiotics were given for a total period of 7-day. The primary outcome measure was "Treatment failure" defined as reappearance of sepsis within 15 days of stopping antibiotics.

Result: A total of 105 babies in the intervention group and 101 babies in the control group were analyzed in the study. Only 40 babies were enrolled in the 1000-1500 g strata and the rest 166 were in the >1500 g strata. Baseline variables were balanced in the 2 groups. There was no significant difference in the treatment failures between the 2 groups (7 in intervention; 5 in control).

Conclusion: The treatment failure rate with a short course of antibiotic (48-96 h) was not worse than that with a 7-day course of antibiotic in preterm babies with probable sepsis.

Key words: Antibiotic duration, Preterm, Probable sepsis, Treatment failure

INTRODUCTION

Neonatal sepsis is a common cause of neonatal mortality and significant morbidity especially neurodevelopmental delay and increased hospital stay.[1] The clinical presentation is very variable and non-specific and based on clinical suspicion; empirical antibiotic therapy is usually initiated after taking blood cultures. In this scenario, many babies who are not actually infected receive unnecessary antibiotics during nursery stay.[2] Prolonged and injudicious use of antibiotics have been found to be associated with increased mortality and necrotizing enterocolitis especially in very low birth weight (VLBW),[3] increased hospital expenditure, mother-baby separation and emergence of drug resistant strains.[4-6]

Pediatric textbooks recommend a treatment duration ranging from 7 to 14 days for blood culture positive or clinically probable infections.[7-9] However, there is no standard evidence-based guidelines as to the appropriate duration of antibiotic therapy for probable neonatal septicemia (non-culture proven). Shorter duration of

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Corresponding Author: Dr. Rajesh Bansal, Flat No. B/8, Rohilkhand Medical College Campus, Pilibhit Bypass Road, Bareilly - 243 006, Uttar Pradesh, India. Mobile: +91-9837235064/9927107555. E-mail: drrajesh29@rediffmail.com

antibiotic therapy may help reduce the above mentioned adverse effects. We made a hypothesis that 7-day antibiotic course in probable neonatal sepsis was unnecessarily long. With this perspective, this study was conducted to assess whether stopping antimicrobials earlier amounts to higher treatment failure compared to conventional 7 days therapy in preterm babies.

METHODS

The study was conducted in the Department of Pediatrics, in a tertiary care teaching hospital in North India. It was an open-labeled, controlled, prospective, randomized trial conducted between February 2014 and February 2016. The study was approved by the Institutional Ethics Committee. All consecutively admitted preterm babies, whether intramural or extramural, with birth weight >1000 g and gestational age more than 30 weeks, with probable neonatal septicemia were eligible for the study. Both early- and late-onset sepsis were included. The exclusion criteria were infants with meningitis, suspected deep-seated infections, severe birth asphyxia, major congenital malformations, and those already on antibiotics or undergoing surgery.

Probable sepsis was diagnosed by history of refusal to feed, poor suck, lethargy, or increased irritability for more than 6-8 h along with a positive C-reactive protein [CRP] >10 mg/L. Blood cultures and complete blood counts were done in all patients. The cerebrospinal fluid (CSF) analysis was done in suspected meningitis and in all cases of late-onset sepsis.[10] Relevant antenatal, natal and postnatal histories, demographic and clinical details were recorded prospectively in a pre-designed per forma. An informed consent was taken from parents of every baby.

The randomization criteria were resolution of clinical signs of sepsis, sterile blood culture reports after at least 48-96 h of incubation, and normal CSF analysis. Randomization was done after 48-96 h of enrollment. The upper limit of 96 h was kept to account for the occasional delay in reporting over weekends or non-office hours.

Eligible babies were randomly allocated in a 1:1 ratio into two groups: Short-course group and 7-day group. Slips of paper bearing computer-generated random allocation sequence were placed in serially numbered, opaque and sealed envelope for concealment of allocation. Every time a patient got enrolled, the opaque envelope was opened and the intervention was executed. In the short-course group, antibiotics were stopped immediately after negative culture report, whereas the 7-day group received full 7-day course of antibiotic.

As a unit protocol, we start all patients with early-onset sepsis on ampicillin and gentamycin, and late-onset sepsis on cloxacillin and gentamycin, pending on blood culture and sensitivity report. Cephalosporins as empiric choice are limited to selected cases of suspected meningitis and suspected nosocomial infections. Routine and supportive cares were provided, as per unit guidelines, to patients of both the groups without any differentiation. All babies received breast milk, either direct or expressed. On completion of antibiotic course, all patients were stringently followed, for evidence of sepsis, for an observation period of 15-day in the outdoor high-risk neonatal clinic. All subjects were called on a weekly basis/SOS. On each visit, parents were questioned regarding episodes of illness during the previous week and followed by physical examination of the baby. A detailed structured pro forma was filled for all such episodes. A sepsis screen, blood culture, chest X-ray, CSF, and other relevant work up were done for all such episodes. For subjects who could not turn up for follow-up were questioned on phone and asked to report to the unit for any episode of illness until 15 days. A two-member, blinded, adjudication committee of senior neonatologists reviewed these forms and gave their opinion independently as to whether the episode of illness represented bacterial sepsis. In cases where their opinions were divided, a consensus was arrived upon by mutual consultation.

The primary outcome variable was "treatment failure" occurring within 15 days of stopping antibiotics and was defined as reappearance of symptomatology suggestive of sepsis, along with laboratory evidence and judged to be relapse by a blinded expert committee.

Statistical Analysis

The baseline variables were described by descriptive statistics. As all outcome variables were categorical, χ^2 test with Yates correction or Fisher's exact test, as applicable, was used. $P < 0.05$ was taken as significant. We analyzed subjects as per intention to treat. The analysis was done using SPSS version 13.0 and Microsoft Excel 2003.

RESULTS

A total of 587 neonates fulfilled the inclusion criteria (Figure 1). 59 babies were excluded. 312 babies did not meet the randomization criteria. The remaining 216 were randomly allocated on a 1:1 basis into short-course antibiotic ($n = 108$) and 7-day antibiotic groups ($n = 108$). During the follow-up period, 3 babies in the short-course group and 7 in the 7-day course group could be contacted. Hence, only 105 babies in the 1st group and 101 babies in

the 2nd group were analyzed in the study. Only 40 babies were enrolled in the 1000-1500 g strata and the rest 166 were in the >1500 g strata.

Baseline variables were comparable in either group (Table 1). There was no significant statistical difference in gestational age, body weight, age of onset, and duration of symptoms between the short-course and 7-day course groups. Maternal risk factors for sepsis, Apgar scores, and EOS:LOS ratio were also comparable between the two groups. All babies analyzed in both the groups completed their entire course of antibiotics with full compliance. Antibiotic usage was similar in both the groups except that more babies in the short-course group received ampicillin. More babies in 7-day course group received cloxacillin (Table 2). All other supportive interventions were similar in both the groups.

Seven babies (6.67%) in the short-course group and five babies (4.95%) in the 7-day group had treatment failure ($P = 0.82$). In the short-course group, six out of the seven treatment failures had late-onset sepsis; whereas, in the 7-day course group all the five babies belonged to late-onset sepsis group. All the treatment failure patients from both the groups were readmitted and managed on standard guidelines. There were no expiries in either group.

DISCUSSION

Only symptomatic babies were included in the study. Babies born with maternal risk factors but asymptomatic were not included in the study, as they were more likely to have shown a positive response, irrespective of antibiotic duration. A similar criterion was used by Saini *et al.*[11] This is in contrast to other studies which enrolled babies irrespective of presentation based on serial CRP measurements.[12-15] We included only VLBW and LBW preterm babies in our study. This was different from the previous study by Saini *et al.*,[11] which included all babies above 1000 g and more than 30 weeks of gestation. We did not include babies less 1000 g as the clinical presentation of sepsis in these babies is often subtle and can be easily missed, both at the time of diagnosis as well as when deciding when to stop antibiotics.

CRP was used at admission as a marker for sepsis. Serial CRP measurements were not employed to ascertain antibiotic duration in our study. Several studies in the past have shown that CRP is a useful guide in deciding duration of antibiotic therapy in neonatal sepsis;[12-15] whereas Al-Zwaini *et al.*[16] reported

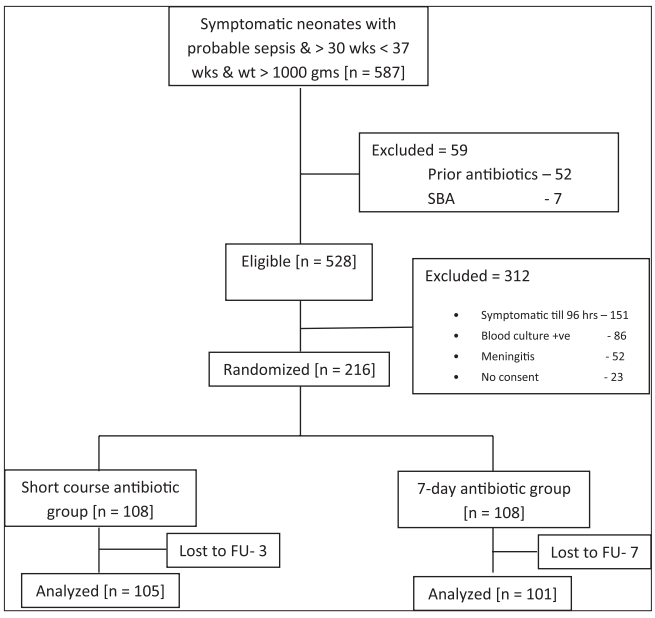

Figure 1: Study flow

Table 1: Comparison of baseline variables

Variables	Short-course group (*n*=105)	7-day group (*n*=101)
Gestation age (weeks) (Mean±SD)	34.7±3.6	35.1±3.8
Body weight (g), median (IQR)	1752 (1521, 2479)	1997 (1596, 2560)
Age of onset of symptoms (h), median (IQR)	21 (1, 95)	50 (0, 329)
Enrollment (d), median (IQR)	3 (2, 4)	4 (1, 14)
Randomization (d), median (IQR)	6 (4, 8)	6.5 (3, 17)
Duration of symptoms (h) (mean±SD)	48.1±24.7	40.9±24.2
Early onset sepsis: Late onset sepsis	71:34	52:49
1 min APGAR score, median (IQR)	8 (6, 8)	8 (6, 8)
5 min APGAR score, median (IQR)	9 (8, 9)	9 (8, 9)
Rupture of membranes>24 h (%)	15 (14.29)	11 (10.89)
Maternal fever (%)	17 (16.19)	2 (1.98)
History of instrumentation (%)	4 (3.81)	2 (1.98)
MSAF (%)	26 (24.76)	19 (18.81)

SD: Standard deviation, IQR: Interquartile range, MSAF: Multi-source assessment and feedback

Table 2: Comparison of co-interventions

Co-intervention	Short-course group *n*=105 (%)	7-day antibiotic group *n*=101 (%)	*P* value
Ampicillin	71 (61.62)	52 (51.49)	0.0183*
Gentamicin	105 (100)	101 (100)	0.7805
Cloxacillin	30 (28.57)	43 (42.57)	0.0357*
Cefotaxime	4 (3.81)	6 (5.94)	0.6986
Supplemental oxygen	21 (20)	26 (25.75)	0.4146
CPAP	68 (64.76)	57 (56.44)	0.28
DVET	11 (10.48)	8 (7.92)	0.6945
Plasma products	3 (22.63)	5 (4.95)	0.6769
Dextrose	101 (96.19)	98 (97.03)	0.9583

**P*: Significant, CPAP: Continuous positive airway pressure, DVET: Double volume exchange transfusion

CRP to be a poor guide for the duration of treatment in neonatal septicemia. Furthermore, repeated CRP estimations lead to increased cost burden on the attendants, especially in a developing country like ours. In our study, randomization was done at 48-96 h only when the culture reports were sterile and the baby was totally asymptomatic. Similar observations were made in previous studies.[11,12,17,18] Randomization was not attempted earlier as it is impossible to predict which baby would become asymptomatic before the availability of culture report. Similarly, during randomization and symptomatic babies were excluded as it is impossible to rule out persistence of infection in them and hence merit further continuation of antibiotics.

With the aim to reduce subjective error, "treatment failure" was confirmed only after adjudication by two senior neonatologists, blinded to each other. Stringent measures were taken to ensure not to miss out treatment failure and all such patients were diligently managed at our hospital. Treatment failure was comparable between the short-course antibiotic and 7-day course groups. There was no statistically significant difference in the treatment failure rate in the two groups. Similar results have also been reported earlier. Cordero *et al.*[19] reported that empiric antibiotics can be safely discontinued when blood cultures are negative in asymptomatic extremely low birth weight neonates. In a study on term and near-term babies with pneumonia, Engle *et al.*[17] compared 4-day versus 7-day antibiotic course and reported similar rate of success in both the groups. In a pilot study by Saini *et al.*[11] done on babies more than 30 weeks and above 1000 g with suspected sepsis found no difference in failure rate between short-course (48-96 h) and 7-day antibiotic course. An interesting observation was that majority of the children with treatment failure in both the groups had late-onset sepsis. A possible explanation for slightly more children being involved in the short-course group could be that babies in this group were relatively more premature and lighter in weight. A sampling error cannot possibly be ruled out as the sample size in our study is too small to document with authority that a short course of antibiotic is not "inferior" to the standard 7-day course. However, the comparable rates of treatment failures in the short-course (6.67%) and in the 7-day course groups (4.95%), which was statistically insignificant, was reassuring that the short course of antibiotic was not worse than the conventional 7-day course, at least in this limited sample size. Hence, further studies are recommended with a comparatively larger sample size so as to qualify for a non-inferiority trial. Our study also throws up a note of caution that although there was no statistically significant difference in the treatment failure rates between a short-course and a 7-day course of antibiotics in preterm babies more than 30 weeks of gestation with probable sepsis, treatment failures occurred maximally in babies with late-onset sepsis in both the groups.

CONCLUSION

This study tries to clear the air regarding the dilemma of optimal duration of antibiotic therapy in a preterm baby with probable sepsis who becomes rapidly asymptomatic following institution of antibiotic therapy. The treatment failure rate with a short course of antibiotic (48-96 h] was not worse than that with a 7-day course of antibiotic.

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