RESEARCH PAPER

Short Course *Versus* 7-Day Course of Intravenous Antibiotics for Probable Neonatal Septicemia: *A Pilot, Open-label, Randomized Controlled Trial*

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Received: September 9, 2009; Initial review: October 9, 2009; Accepted: January 28, 2009.

Objective: To compare a short course of antibiotics (48 to 96 hours) and a standard course of antibiotics (7 days) for probable neonatal sepsis.

Design: Randomized, controlled, open-labeled trial with blocking and stratification according to birth weight.

Setting: Tertiary care, referral, teaching hospital in Northern India.

Participants: Neonates >30 wks gestation and >1000 g at birth, with probable sepsis (clinical signs of sepsis, raised C-reactive protein) were enrolled. Babies with major malformations, severe birth asphyxia, meningitis, bone or joint or deep-seated infection, those who were already on antibiotics, and those undergoing surgery were excluded. Neonates, who had clinically remitted on antibiotic therapy – by the time a sterile blood culture report was received – were randomized.

Intervention: In the intervention arm, antibiotics were stopped after the 48-hour culture was reported sterile. In the control arm, antibiotics were continued to a total of 7 days.

Main outcome measure: "Treatment failure" defined as reappearance of signs suggestive of sepsis within 15 days of stopping antibiotics, supported by laboratory evidence and adjudicated by a blinded expert committee.

Results: 52 neonates were randomized to receive a short course or 7-day course (n=26 each). Baseline variables were balanced in the 2 groups. There was no significant difference in the treatment failures between the 2 groups (3 babies in the 7-day group *vs* none in short course group, P=0.23).

Conclusion: No difference in the treatment failure rates could be identified between short course and 7-day groups among neonates >30 weeks and >1000 grams with probable sepsis.

Key words: *Antibiotics, Duration, Neonatal sepsis, Short course, Treatment failure.*

Published online: 2010 August 1. PII: S097475590900636-1

Duration of appropriate antibiotic therapy for neonatal sepsis does not have evidence-based guidelines. Standard textbooks recommend treatment end points of 7-14 days for blood culture positive or clinically probable infections [1-3]. The rationale and safety of these recommendations have never been scientifically evaluated.

Such untested approaches could result in the unnecessary use of antibiotics leading to increased cost of care, unnecessary intravenous catheterization, prolonged hospitalization, mother-infant separation, increased colonization by pathogenic organisms and emergence of drug-resistant strains [4-7]. A shorter duration of antibiotic therapy may benefit by decreasing the above undesirable consequences [8]. We hypothesized that 7 days of antibiotics might be too long in cases of probable neonatal sepsis. The protection offered by longer

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duration of antibiotics may be offset by the above mentioned drawbacks.

Considering the ambiguity in the existing literature about guidelines for the duration of antibiotic therapy for probable (i.e. non-culture-proven) neonatal sepsis, we conducted this trial to determine whether a policy of stopping antibiotics early incurs a significantly higher treatment failure rate than conventional seven days therapy.

METHODS

This was a controlled, open-label, randomized trial with stratification and blocking, conducted between September 2006 to November 2007 at a Level III neonatal unit in Northern India. The unit has a large referral load and caters to a middle-to-low socioeconomic population. The study was approved by the Institute's Ethics Committee.

All inborn or outborn neonates, admitted in the Neonatal Unit with birth weight >1000 grams and gestation age >30 weeks, who were started antibiotics for probable sepsis were eligible for study. Both early onset and late onset sepsis were included. The diagnosis of probable sepsis was based on the presence of a repertoire of clinical symptoms and signs over duration of at least 6 hours and a positive C-reactive protein (CRP) test. The clinical signs were recorded by the chief investigator. Positive CRP was defined as presence of agglutination at a dilution of ≥1:2 by a semi-quantitative latex agglutination test (Teco Diagnostics, 1268, N Lake view Ave, Anaheim, CA. 92807 USA), which corresponded to a CRP titre of ≥12 mg/L. Babies with major congenital malformations, severe birth asphyxia (defined as Apgar score ≤3 at 5 minutes), meningitis [9], clinically suspected bone/joint/deep seated localized infection, those who were already on antibiotics for a previous episode of sepsis, and those undergoing surgery were excluded from the study.

An information sheet providing the details of the study was provided to the parents. Identification, demographic and clinical details of the sepsis episode and CRP results were recorded in a structured case report form after taking written informed consent.

Sample size: Ideally, this research question merits a non-inferiority trial where sample sizes are huge. Baseline treatment failure rate after 7 days of antibiotics for probable sepsis is not reported in literature. Hence we planned to have a sample size of 50 patients as a pilot study. To account for 10% loss during follow up, we decided to recruit 55 patients.

Randomization was done between 48 and 96 hours after the enrollment, if the following randomization criteria were fulfilled: Clinical signs of sepsis had remitted; Blood culture was reported sterile after 48 hours or more of incubation. (An upper limit of 96 hours for reporting was kept to account for the occasional delay in reporting over weekends or non-office hours); and CSF analysis was not suggestive of meningitis [9].

Stratification was done for birth weight (1000-1500 g and >1500 g). Each stratum consisted of permuted blocks of randomly varying sizes. Eligible babies were randomly allocated in a 1:1 ratio to one of the two groups: *Short-course group*: these subjects did not receive further antibiotics after receiving the blood culture report, or *7-day group*: these subjects received a total of 7 days of antibiotics. The random allocation sequence was computer generated and slips of paper bearing the allocated intervention were placed in serially numbered, opaque, sealed envelopes to ensure concealment of allocation. One of the investigators generated the allocation sequence and another enrolled and assigned participants. As consecutive patients got enrolled, the opaque envelope was opened and the intervention was executed.

Routine and supportive care was provided in a similar fashion to patients in both groups as per unit guidelines. Antibiotics were prescribed as per the policy prevalent in the unit at that time. The use of breast milk is aggressively promoted in our unit. Intra-venous fluids are stopped once milk intake crosses 100-120 mL/kg/day.

We monitored the subjects for episodes of sepsis in follow-up. The period of observation was 15 days after completion of antibiotics. All subjects were followed up by weekly appointments. At each visit, information regarding episodes of illnesses in the previous week was recorded by the chief

investigator. If any subject did not come for follow-up, they were contacted by telephone. Parents were asked to report to our unit for any episode of illness till 15 days. The clinical signs and symptoms were noted by chief investigator and a detailed structured proforma 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. A two-member, blinded, adjudication committee of experienced neonatologists reviewed these forms and masked chest radiographs. Each member gave his/her opinion independently whether the episode of illness represented bacterial septicemia. In cases where they held divergent opinions, a consensus was arrived upon by mutual consultation.

*Outcome variables:*The key outcome variable was "treatment failure" occurring within 15 days of stopping antibiotics and was defined as reappearance of signs suggestive of sepsis, supported by laboratory evidence and adjudicated 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, were used. *P* value <0.05 was taken as significant. We analyzed subjects as per intention to treat. Analysis was done using SPSS version 13.0 and Microsoft Excel 2003.

RESULTS

Out of 305 neonates who fulfilled the inclusion criteria (***Fig.* 1**), only 65 met exclusion criteria and 188 could not meet randomization criteria. Hence, 52 babies were randomly allocated to the short-course and the 7-day antibiotic group (26 babies each). Ten babies got enrolled in the 1000-1500 grams and 42 in the >1500 grams strata. Baseline variables were comparable between the two study groups (***Table* I**). No baby received TPN during study period. All cases, randomized to either group, completed their respective courses of appropriate antibiotics with full compliance. Over the 15 days follow-up period, there was 1 loss to follow-up in each group.

The two groups were balanced in terms of the signs and symptoms of sepsis at presentation. The use of antibiotics was similar between the two groups. Group 2 neonates received Amikacin more often than group 1 (*P*=0.03). A greater number of babies in the short-course group received supplemental oxygen, whereas more babies in the 7-

TABLE I COMPARISON OF BASELINE VARIABLES

Baseline variable	Short-course group (*n*=26)	7-day group (*n*=26)
Gestational age (wks), Mean ± SD	34.9 ± 3.3	34.6 ± 3.4
Birthweight (g), Median (IQR)	1900(1627, 2478)	1687(1504, 2450)
Age at onset of symptoms (hrs), Median (IQR)	19 (0, 96)	47 (1, 342)
Enrollment (d), Median (IQR)	3 (1, 4)	3 (2, 15)
Randomization (d), Median (IQR)	5.5 (4, 8)	6 (4, 18.25)
Duration of symptoms (hr), Mean ± SD	48.0 ± 24.4	58.7 ± 24.1
EOS:LOS	17:9	17:9
1 Min Apgar, Median (IQR)	8 (6, 8)	8 (7, 8)
5 Min Apgar, Median (IQR)	9 (8, 9)	9 (8, 9)
Rupture of membranes ≥24 hours	3 (11.5%)	3 (11.5%)
Maternal fever	3 (11.5%)	0
Mothers received antibiotics before delivery	7 (27%)	3 (11.5%)

EOS: early-onset sepsis; LOS: late onset sepsis; IQR: Interquartile range.

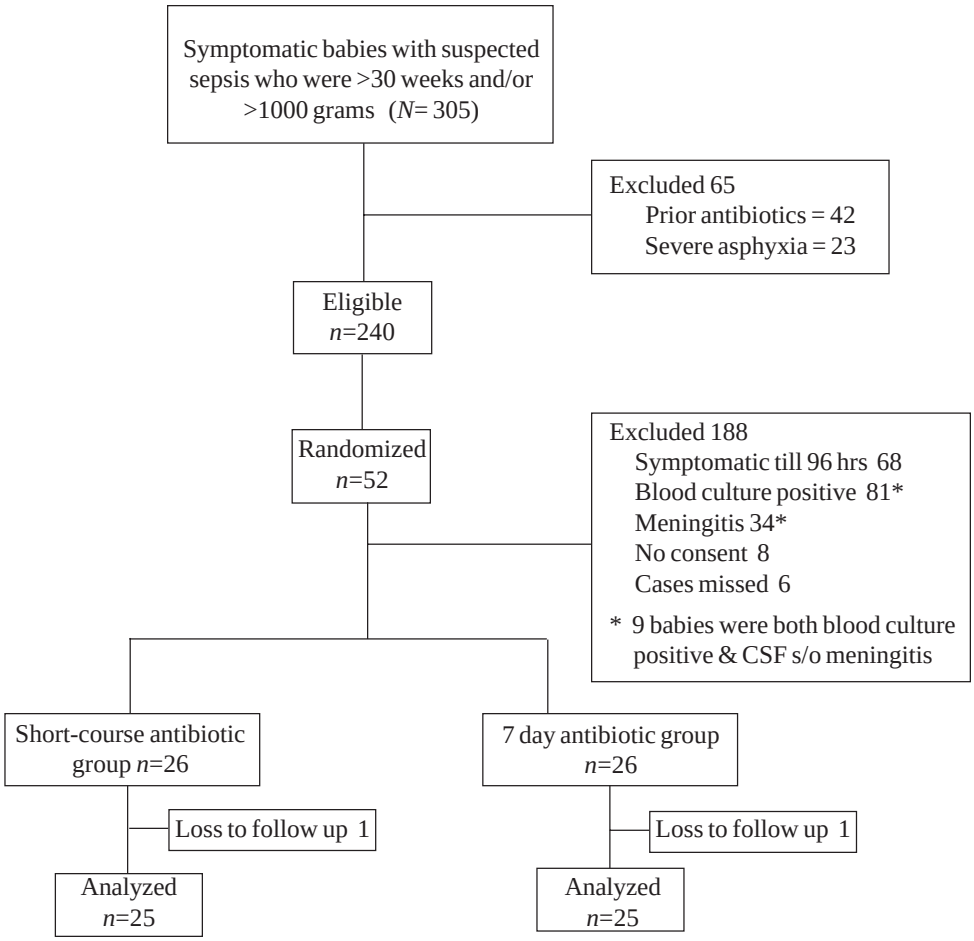

Fig. 1 *Study flow*.

day group received continuous positive airway pressure (CPAP). All other supportive interventions were used in similar proportions in the two groups. (***Table* II**).

Three babies in the 7-day group had treatment failure as opposed to none in the short-course group (*P*=0.23). One baby developed apnea 10 days after stopping antibiotics. His blood culture grew methicillin resistant *Staphylococcus aureus*. Another baby got admitted with complaints of lethargy, poor feeding and diarrhea 10 days after stopping antibiotic therapy and had evidence of meningitis (50 white blood cells per µL, all neutrophils). Both babies recovered on antibiotic therapy. The third baby was discharged on day 13 of life (4 days after stopping antibiotics) and was asymptomatic at discharge. The baby died unexpectedly at home a couple of days later.

DISCUSSION

In this study, there was no significant difference in the treatment failure rates with short course and 7 days of antibiotics for uncomplicated probable neonatal sepsis. Hence it generates the possibility of shortening of duration of antibiotic therapy in probable neonatal sepsis.

We included only symptomatic babies and did not include asymptomatic babies with maternal risk factors as they are likely to have a very low baseline event rate and would show a favorable response irrespective of duration of antibiotics. This is in contrast to previous serial CRP based studies which included babies irrespective of symptomatology [10-13]. We excluded extremely low birth weight babies as they often have subtle signs of sepsis which can be clinically missed and various other neonatal diseases

TABLE II COMPARISON OF CO-INTERVENTIONS

Co-intervention	Short-course group (*n*=26)(%)	7-days group (*n*=26)(%)	*P* value
Any cephalosporin	24 (92.3)	24 (92.3)	1.00
Amikacin	18 (69.23)	24 (92.3)	0.03
Cloxacillin	6 (23.07)	1 (3.8)	0.10
Supplemental oxygen	14 (53.85)	5 (19.23)	0.02
CPAP	1 (3.8)	8 (30.8)	0.02
NIMV	1 (3.8)	1 (3.8)	1.00
Any respiratory support	16 (61.5)	12 (46.15)	0.26
DVET	1 (3.8)	1 (3.8)	1.00
Plasma products	1 (3.8)	1 (3.8)	1.00
Dextrose infusion	1 (3.8)	0	1.00

Figures in parentheses are percentages; CPAP- continuous positive airway pressure, NIMV- Nasal intermittent mandatory ventilation, DVET- Double volume exchange transfusion.

may mimic sepsis, making the evaluation of treatment failure a difficult exercise. We used CRP (at presentation) as a marker of sepsis and did not use serial CRP values to stop antibiotics, so that the results could be generalized to even resource-poor areas, where laboratory facilities are not easily available.

In the present study, randomization was done only if the babies had become completely asymptomatic. It would be impossible to exclude persisting infection with reasonable certainty in symptomatic babies and, thus, would be unethical to stop antibiotics. We did not randomize at the beginning of the antibiotic course because there was no way of predicting which babies would become asymptomatic by the time the culture report was available. This study replicated the state of clinical dilemma (regarding continuation of antibiotics) that exists after a baby who had suspected sepsis with raised CRP, becomes asymptomatic soon after starting antibiotics.

An upper limit of 96 hours was decided based on the observations made in previous studies [10,14]. To minimize measurement bias, the diagnosis of "treatment failure" in our study was adjudged by two blinded neonatologists. Since the study entailed a new regimen of a potentially fatal disease, we took special measures to ensure that the treatment failures were not missed.

The non-significant trend of higher treatment failures in the 7-day group was, if anything, reassuring, that in this limited sample the short course regime was not worse than the 7-day regime. The possible reason of the increased treatment failures could be presence of IV cannula for a longer duration in 7 days group, when it was not required. Although the two groups were balanced in terms of baseline variables, neonates in 7-day group appear to be born lighter and sicker (higher proportion were lethargic, had abdominal distension and poor feeding), which could also partly contribute to the outcome. A sampling error may have occurred due to small sample size. The study has certain limitations. The sample size of our study was too small for us to conclude that a short course of antibiotics is definitely not inferior to a standard 7-day course. Using our study as a pilot study, we estimate the sample size for a non-inferiority trial to be approximately 2700. The results are only valid for the specified subgroup of preterm neonates of >1000 g birth weight and >30 weeks gestation. We could not introduce blinding as it was impractical to prepare identical-looking placebos for a wide range of antibiotics, and arrange for sham antibiotic administration for the short course group. Quantitative CRP assay would have been more useful as a marker for sepsis.

In the current study, there was no statistically significant difference in the treatment failure rates

WHAT IS ALREADY KNOWN?

- Duration of antibiotic therapy for neonatal sepsis has no evidence base, but 7 to 10 days of antibiotics are often prescribed for probable sepsis.

WHAT THIS STUDY ADDS?

- Within the limitations of a small sample size, the treatment failure rate with a short course of antibiotics (between 48-96 hours) was not worse than that with a 7-day course of antibiotics among neonates with probable sepsis, who become rapidly asymptomatic with antibiotic therapy.

between a short course and a 7-day course of antibiotics among preterm neonates >30 weeks and >1000 grams with probable sepsis, who became asymptomatic within 48 to 96 hours of intravenous antibiotics.

Contributors: SSS: Collected data, entered data, did analysis, wrote first draft; SD: Conceived the idea, planned the study, finalized the manuscript; PR: Performed blood cultures; AN: Supervised study, edited the manuscript.
Funding: None.
Competing interests: None stated.

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