Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D. Ma. Lourdes S. Imperial M.D Candice Janine R. Usman, M.

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

INTRODUCTION

BACKGROUND OF THE STUDY

Sepsis is a global public health priority due to its fatal outcomes in extreme age groups, such as newborn. Any systemic bacterial infection documented by a positive blood culture in the first month of life is referred to as neonatal sepsis. Early-onset neonatal sepsis refers to cases in which clinical manifestations appear within the first 72 hours of life and are considered limited within the first seven days.

The clinical assessment of neonatal sepsis is difficult; some neonates are at risk of delayed recognition of sepsis until more dangerous clinical findings and vital sign abnormalities appear. The keys to successful treatment are early diagnosis, timely antibiotic administration, and appropriate supportive management. Although there is agreement among authors that antibiotic therapy should be started as soon as neonatal sepsis is suspected, there is no agreement on the duration of treatment.

There is a wide range of current practices, and there are still disagreements about the duration of antimicrobial therapy. 1 It is a common practice to discharge newborns only after 7 days of antibiotics is completed, even though their final blood cultures are negative after 5 days of incubation. A review of this practice is warranted in order to reduce hospital stay, unnecessary antibiotic exposure and excessive family expenses.

An average of 3 to 5 days of antimicrobial therapy for culture-negative asymptomatic extremely low birth weight infants was investigated in a study in 2004, and it showed that the shorter course can be used without compromising the clinical outcome 14 . On the other hand, here in our country, a lack of evidence supporting short-course antibiotic treatment led to the recommendation of completion of 7 days of therapy in the 2019 Clinical Practice Guidelines for the Screening, Diagnosis, Treatment, and Prevention of Neonatal Sepsis. More studies on the appropriate duration of antimicrobial therapy is needed to inform neonatal sepsis treatment strategies in the Philippines.

OBJECTIVES OF THE STUDY

GENERAL OBJECTIVE

This study aims to compare the Outcome of neonates with blood culture-negative neonatal sepsis treated with a 5-day vs 7-day course of intravenous antibiotics.

SPECIFIC OBJECTIVES

- Determine the demographic profile of blood culture negative neonates.
- Compare the outcomes in the 5-day course group vs the 7-day course group in terms of: Laboratory results, signs and symptoms both on admission and on follow upand number of readmission.

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.DMa. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

METHODOLOGY

STUDY DESIGN

Single-Blind randomized control study.

STUDY SETTING

This study was conducted from May, 2022 to December, 2022 in a tertiary government hospital in Quezon City, National Capital Region, Philippines

PATIENT SELECTION

INCLUSION CRITERIA:

All term neonates admitted either in the NICU or Sick Neonate Ward within the first 7 days of life with the diagnosis of neonatal sepsis with negative blood culture growth

EXCLUSION CRITERIA:

1. Neonates born with major congenital malformations
2. Neonates with severe asphyxia (Severe Acidosis pH <7.0, Apgar score 0-3 after 5 minutes of life, Neurological problems such as seizures, coma and no spontaneous movement, signs of low blood flow in organs such as kidney and intestines.)
3. No consent from the guardian allowing the neonate to be included in the study

WITHDRAWAL CRITERIA:

1. Neonates born with major congenital malformations
2. Neonates with negative blood culture result but with signs of progression of sepsis (need of oxygen support, signs of bleeding, seizures, tensed, bulging of fontanels, unexplained abdominal distension, decreased spontaneous movement and coma.)
3. Failure to follow up after treatment

CLINICAL CRITERIA FOR THE DIAGNOSIS OF SEPSIS

- Fever (>37.7°C)
- Jaundice
- Poor feeding
- Seizures
- Others: Dermatologic: skin pustules, periumbilical erythema or purulence Musculoskeletal: edema or erythema overlying bones or joints.
- Hypothermia (<35.5°C)
- Respiratory Distress (Respiratory rate >60 breaths/min, grunting, chest in drawing, central cyanosis)
- Poor/ decreased in activity
- Obstetric Risk Factors (Prolonged ruptured membranes, Maternal Infection, Chorioamnionitis).

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Candice Janine R. Usman, M.D
Ma. Lourdes S. Imperial M.D

METHODOLOGY

RANDOMIZATION

The randomization used in this study was based on the single sequence of random assignments. Researcher assigned the participants based on the sequence of their admission. All neonates who fulfilled the inclusion criteria were allocated to one of the following groups:

All odd numbers will be Group A (5-day antibiotic course group) and all even numbers will be Group B (7-day antibiotic course group).

Group A	Group B
Treated with antibiotics (Ampicillin 50mg/kg/dose every 12 hours + Amikacin 15 mg/kg/dose every 24 hours) for 5 days	Treated with antibiotics (Ampicillin 50mg/kg/dose every 12 hours + Amikacin 15 mg/kg/dose every 24 hours) for 7 days

SAMPLE SIZE

The sample size for this study was calculated using Cochran's formula with

30 neonates in

INTERVENTIONS

Patients were randomly assigned to either 5-day or 7-day empiric antibiotic therapy. Laboratory tests were conducted, including baseline CBC and blood culture. Newborns were reassessed during hospital stay, and repeat CBCs were conducted after 3 days. After antibiotic treatment, newborns were discharged, and mothers were provided with discharge instructions. (See appendix B).

COLLECTION OF DATA

The main investigator was in charge of the collection of data in the hospital. All admitted newborns within the first 7 days of life were screened in accordance with the inclusion criteria and those who fulfilled the criteria were recruited into the study. Demographic data was collected and tabulated as presented in Table 1.0. The neonates' guardians and/or parents were asked to give an informed consent.

FOLLOW UP AND MONITORING

The primary caregiver was instructed to create a daily monitoring sheet for 7 days, listing signs and symptoms of sepsis. If symptoms appeared, the caregiver referred the patient to the researcher. Both groups had a one-week observation period, and neonates were required to follow up via OPD Telemedicine 7 days after antibiotics. The caregiver was given mobile load allowance for follow-up consultations.

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

STATISTICAL ANALYSIS:

The Chi test of independence was used mainly to observe significant differences in the newborns' demographic profiles and CBC results. The ANOVA and T test were also used to analyze demographic profile on weights and age of gestations, respectively with p value <0.05 since these were not categorical data sets.

A total of 30 eligible neonates were enrolled in the study. Demographic characteristics were comparable between the 2 groups (Table 1). Majority of the recruited subjects were term neonates at 39 weeks of gestation while minority were at 37 weeks, being 2 from those who received 5-day course and 3 from those who had 7-days of treatment. Most of the participants weighed between 2500-2999 grams for both groups, while only 2 from the 7 days' treatment group weighed between 2000-2499 grams. There was no significant difference in the sex, manner of delivery and APGAR score between 2 groups. Cases of prolonged rupture of membranes were the highest number of maternal risk

RESULTS

TABLE 1. DEMOGRAPHIC PROFILE

CHARACTERISTICS	5-DAY COURSE (N= 15)	7-DAY COURSE (N=15)	P VALUE
GESTATIONAL AGE (WEEKS)			
37 WEEKS	2	3	0.36
38 WEEKS	5	5	
39 WEEKS	8	5	
40 WEEKS	0	1	
41 WEEKS	0	1	
BIRTH WEIGHT (GRAMS)			
2000-2499 GRAMS	0	2	0.13
2500-2999 GRAMS	8	8	
3000-3499 GRAMS	5	5	
3500-3999 GRAMS	2	0	
SEX			
MALE	10	7	0.40
FEMALE	5	8	
MODE OF DELIVERY			
NSD	8	7	0.60
CS	7	8	
APGAR SCORE: T 1 MINUTE			N/A
1	0	0	
2	0	0	
3	0	0	
4	0	0	
5	0	0	
6	0	0	
7	0	0	
8	0	0	
9	15	15	
10	0	0	
5 MINUTES			
1	0	0	
2	0	0	
3	0	0	
4	0	0	
5	0	0	
6	0	0	
7	0	0	
8	0	0	
9	15	15	
10	0	0	
10 MINUTES			
1	0	0	
2	0	0	
3	0	0	
4	0	0	
5	0	0	
6	0	0	
7	0	0	
8	0	0	
9	0	0	
10	15	15	
MATERNAL RISK FACTORS			
CHORIOAMNIONITIS	3	1	0.41
MATERNAL FEVER (T> 37.8°C)	1	1	0.68
MATERNAL LEUKOCYTOSIS	0	0	N/A
MATERNAL UTI	2	3	0.57
PROLONGED RUPTURE OF MEMBRANES	12	14	0.41
SIGNS AND SYMPTOMS OF SEPSIS			
ASYMPTOMATIC	10	12	
FEVER (T> 37.8° C)	4	1	
POOR FEEDING	1	0	
CYANOSIS	0	1	
JAUNDICE	0	1	

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

RESULTS

TABLE 2. COMPARISON OF COMPLETE BLOOD COUNT WITH PLATELET COUNT RESULTS UPON ADMISSION AND ON DAY 3 OF ANTIBIOTICS

COMPLETE BLOOD COUNT	5-DAY COURSE (N=14)		7-DAY COURSE (N=13)		P VALUE
	ADMISSION	DAY 3	ADMISSION	DAY 3	
WHITE BLOOD CELLS (WBC)					
LEUKOCYTOSIS	3	0	5	0	0.68
NORMAL LEVEL OF WBC COUNT	11	14	6	13	
LEUKOPENIA	0	0	2	0	
PLATELET COUNT					
THROMBOCYTOSIS	3	2	6	4	0.36
NORMAL LEVEL OF PLATELET COUNT	11	12	7	9	
THROMBOCYTOPENIA	0	0	0	0	
ABSOLUTE NEUTROPHILIC COUNT (ANC)					
HIGH ANC	5	0	8	0	0.68
NORMAL ANC	9	14	3	13	
LOW ANC	0	0	1	0	

The majority of the neonates in both groups had normal WBC levels both on admission and on day 3 of antibiotics (Table 2).

Three neonates in the 5-day course of antibiotics initially had increased WBC, as did five in the 7-day course group. The majority of neonates in both the 5-day and 7-day treatment groups had normal platelet counts and ANC. None of the infants in either group developed thrombocytopenia, although two had leukopenia at admission from the 7-day course group. Overall, complete blood count differences between the 2 groups were not statistically significant on admission and on day 3 of antibiotic administration.

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.DMa. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

RESULTS

TABLE 3. COMPARISON OF SIGNS AND SYMPTOMS ON ADMISSION AND ON FOLLOW UP 7 DAYS AFTER DISCHARGE

SIGNS AND SYMPTOMS	5-DAY COURSE (N=14)		7-DAY COURSE (N=13)	
	ADMISSION	ON FOLLOW UP	ADMISSION	ON FOLLOW UP
ASYMPTOMATIC	9	14	10	13
FEVER	4	0	2	0
JAUNDICE	0	0	2	0
RESPIRATORY DISTRESS	0	0	1	0
POOR FEEDING	1	0	0	0
POOR ACTIVITY	0	0	0	0
PALLOR	0	0	0	0
SEIZURE	0	0	0	0

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

RESULTS

TABLE 4. COMPARISON OF FINAL OUTCOMES

OUTCOME	5-DAY COURSE (N=14)	7-DAY COURSE (N=13)
SYMPTOMATIC	0	0
WELL (ASYMPTOMATIC)	14	13
RE-ADMITTED	0	0

In both groups, patients who were asymptomatic from the day they were admitted remained asymptomatic until after the follow-up period. Patients who presented with fever, poor feeding, and jaundice on admission did not show any recurrence of symptoms during follow-up for either the 5-day or 7-day course groups. All neonates included in this study were all discharged well in both the 5-day and 7-day course groups (Table 4).

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

RESULTS

TABLE 5. NUMBER OF DROPOUTS AFTER RANDOMIZATION FROM BOTH THE 5 -DAY AND 7-DAY COURSE OF ANTIBIOTIC TREATMENT GROUPS.

GROUP	NUMBER OF SAMPLES	REMARKS	MARGIN OF ERROR
GROUP A (ANTIBIOTICS FOR 5-DAYS)	14	1 DROP OUT AT DAY 1 AND 1 WITHDRAWN FROM STUDY	25% TO 26% (1% INCREASE)
GROUP B (ANTIBIOTICS FOR 7-DAYS)	13	1 DROP OUT AT DAY 5; NO FOLLOW UP DONE	25% TO 27% (2% INCREASE)

There were three newborns who dropped out during the research period. There were two dropouts from the 7-day treatment group, one owing to withdrawal of consent from the first day of antibiotics and the other following the discovery of congenital heart disease on the 7th day of life, causing an increase in the margin of error from 25% to 27%. On the other hand, there was one dropout from the 5-day treatment group due to lack of follow up, increasing the margin of error by 1% (Table 5).

Quirino Memorial Medical Center
Department of Pediatrics

A COMPARISON OF A 5-DAY VS 7-DAY COURSE OF ANTIBIOTICS FOR EARLY-ONSET CULTURE-NEGATIVE NEONATAL SEPSIS IN TERM INFANTS IN TERTIARY GOVERNMENT HOSPITAL IN NATIONAL CAPITAL REGION, PHILIPPINES: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

Reynagine E. Aguilon, M.D
Ma. Lourdes S. Imperial M.D
Candice Janine R. Usman, M.D

CONCLUSION

Outcomes of this study were similar in both groups, in terms of improvement in both the laboratory parameters and clinical condition of symptomatic newborns, while asymptomatic infants were noted to have remained well and did not develop signs of sepsis on follow up after 7 days. For potentially septic neonates with mild or no signs of illness, and of with culture negative results, outcomes were comparable and the shorter 5-day course of antibiotic treatment may be appropriate. A shorter antibiotic course will reduce the burden on families caused by prolonged stays and greater hospital expenses, while also adhering to antimicrobial stewardship by reducing antibiotic exposure and offering a safe and acceptable duration of empiric antibiotic

RECOMMENDATIONS

To further advance the study, higher sample sizes may be recommended to reduce the margin of error of the study and extend the experiment to include Day 5 vs Day 7 status of CBC with platelet to compare results at the end of treatment. A longer observation period after completion of antibiotics should be done to cover the whole neonatal period.

Furthermore, C- Reactive Protein and Procalcitonin maybe included as ancillary procedures to exclude the diagnosis of neonatal sepsis.