



Impact of Empirical Antibiotic Treatment Duration on Short-term Prognosis of Very Low Birth Weight Newborns

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Abstract

Objective: Probable early infection is one of the most important reasons to begin antibiotics treatment for very low birth weight (VLBW) infants. In most of the cases, antibiotics treatment continues as long as the venous line persist. Long-term empirical antibiotics therapy for premature infants (5 days) create even more danger than the infection itself, such as necrotizing enterocolitis (NEC) and death. In order to reduce the risks of these dangers, antimicrobial therapy must stop in clinical conditions in which the possibility of infection is low. This study makes an effort to evaluate the impact of empirical antibiotic treatment duration on early prognosis of premature infants with VLBW.

Materials and Methods: A total of 209 premature infants with birth weight less than 1500 g who were suspicious of having infection, were evaluated in 2 groups of control (107 infants) and intervention (102 infants). All of the infants evaluated for sepsis according to the protocol of the unit. In the control group, antibiotics treatment continued as long as the venous line persist, in the intervention group after day 3 to 5 if the results of blood culture were negative, the infants were checked for C-reactive protein (CRP), and if it was negative too and the patient's clinical status was good, antibiotic treatment was stopped. The outcome measures were short-term prognosis of with VLBW newborns.

Results: The mean gestational age of the studied patients was 30.21 ± 2.69 and 29.57 ± 2.09 g in the control and intervention groups, respectively ($P=0.07$). The average days of receiving antibiotics in the control group were 29.21 ± 1.57 while in the intervention group it was 8.11 ± 2.16 ($P<0.001$). Our study suggests that duration of hospitalization ($P<0.001$), need for mechanical ventilation ($P<0.001$) and duration of use of high-flow nasal cannula (HFNC) ($P=0.04$), blood products transfusion ($P=0.007$), length of stay in hospital ($P<0.001$) were dramatically decreased in intervention group comparing to control group. Rate of later sepsis work-ups was decreased as well. But, in other findings such as need for continues positive airway pressure (CPAP), parenteral nutrition, mortality rate, need for resuscitation and rate of urinary tract infection, no meaningful difference were found between two groups ($P>0.05$).

Conclusion: Early discontinuing of antibiotics (5 days or less) had no impact on the mortality rate of VLBW infants and seemed it was safe.

Keywords: Premature infants, Very low birth weight infants, Antibiotic treatment, Early onset sepsis

Introduction

Premature infants are more susceptible to infection. Antibiotics are the most frequent drugs used in neonatal intensive care units (NICUs). Most of the clinicians continue use of antibiotics therapy even in apparently good infants without evidence of infection. However, they are worry about superinfection from the site of IV lines or unreliability of the blood culture results in their settings (1).

In a multicenter survey in 2009 Cotten et al found prolonged use of antibiotics was associated with increased risk of death and necrotizing enterocolitis (NEC) (2). Prolonged administration of empirical antibiotics to premature infants with sterile cultures in the first week of life

was associated with higher risks of late onset sepsis, NEC, and mortality (3).

For reducing these risks, antibiotics should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low. (If the results of blood culture receive during 3-5 days discontinuation of antibiotics should be before 5 days). In Iran most of neonatal units have a liberal use of antibiotics for preterm infants without consideration of negative sepsis workup findings. There are few evidence to report short-term prognosis of very low birth weight (VLBW) infants who receive empirical antibiotics for early onset suspected or proven sepsis in our region.

Therefore, the aim of study was to compare short-term

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prognosis of 2 groups of VLBW infants: long-term empirical antibiotics treatments versus short-term one (less than 5 days).

Materials and Methods

In a randomized controlled clinical trial study hospitalized patients in the NICU of Al-Zahra teaching hospital from January 2013 to June 2015 were studied. Namely 250 premature infants with VLBW were studied.

Preterm newborn infants with birth weight less than 1500 g that were admitted to the NICU with suspected sepsis were randomly enrolled into the study. Most of the infants had respiratory distress and the workup was for rollout of GBS (Group B Streptococci) Infections. Infants with congenital malformations, immunodeficiency disorder, transferring to another hospital during infant's hospitalization, known syndromes, or chromosomal anomalies were excluded from this study.

Sample size was determined based on consideration of the sepsis as outcome measure.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2} = 90$$

It was calculated at least 90 based on odds ratio (OR) = 1.4 using power analysis and sample size (PASS) and regarding 95% CI, 80% power of test, and two-tailed test. Considering 20% sample loss, sample size increased to 108 subjects.

Informed parental consent was obtained when the infant met the inclusion criteria. After getting the permission of their parents, patients were randomly divided into 2 groups. For randomization of the study we used a computer generated randomization list prepared by an independent statistician who not involved in the rest of the investigation.

Patients were randomly divided into 2 groups of control (n = 107) and Intervention (n = 102).

At the beginning of the hospitalization, all of the patients were evaluated for sepsis (blood culture at the entrance and complete blood count [CBC] and C-reactive protein [CRP] at 6-12 hour later, if respiratory distress was found chest X-ray was taken). Then empirical antibiotics, ampicillin and gentamicin, were started with appropriate dose. Second CRP was checked again at 3-5 days after admission with other laboratory tests. In control group, as long as the intravenous line persists, the antibiotics continued to be infused. In the second group (intervention) between days 3 to 5, if the results of the blood culture and second CRP were negative and there were no symptoms of an infection, antibiotics were stopped. It was beside the need to keep intravenous (IV) line for the fluid therapy and total parenteral nutrition (TPN). If the primary laboratory data or clinical condition showed evidences in favor of a suspected or proven sepsis, the use of antibiotics continued accordingly.

The patients followed until patient discharged or death. Primary outcome consist of mortality, NEC (grade 2 or

higher) based on Bell's criterion, intraventricular hemorrhage (IVH) (grade 2 or more), late-onset sepsis (with a positive blood culture), the total antibiotics use days. Secondary outcomes were the duration of hospitalization and bacteriologic information related to bacteria (including the kind of bacteria, antibiogram, allergies and resistances) were registered.

Statistical Analysis

Data was analyzed by SPSS version 17. Kolmogorov-Smirnov test was used for descriptive data; the results were mentioned in the form of mean \pm standard deviation (SD), and frequency (percent).

To see whether there was a statistical relationship or not, statistic tests such as independent samples test, chi-square and Fisher exact test were used. Also in this study, the meaningful level was considered to be less than 0.05.

Results

In this study, 250 infants were included. Finally, due to the presence of exclusion criteria in 41 patients, they were excluded from the study. Finally, 209 neonates completed the study and were randomly divided to the control group (n = 107) or intervention group (n = 102). All of the infants evaluated for sepsis according to the protocol of the unit. Flowchart of participation of subjects in the study was shown in Figure 1.

The mean gestational age of the studied patients was 30.21 ± 2.69 and 29.57 ± 2.09 g in the control and intervention groups, respectively ($P=0.07$). No significant difference was seen in participants' sex distribution or their gestational age between 2 groups (Table 1).

Mortality rate was same between 2 groups. In control group 99 (92.5%) infants were discharged from the hospital and 8 (7.5%) infants died. In the intervention group, 95 (94.1%) infants were discharged and 7 (5.9%) infants died. These differences were not meaningful based on the statistical test of chi-square ($P=0.65$; Table 2)

Blood culture of all the hospitalized infants was prepared routinely. In the control group, 32 out of 107 infants (29.9%), despite negative blood culture results and due to sepsis symptoms, needed a second blood culture, 12 (11.2%) infants needed a third blood culture and 4 (3.7%) infants needed a fourth blood culture.

But in the Intervention group, 8 infants (7.8%) needed a second blood culture and these differences were actually made since antibiotics were cut off very sooner than witness group. These differences were found meaningful based on statistical tests of chi-square (Monte Carlo method) ($P<0.001$).

The duration of hospitalization in the first group was 40.19 ± 1.94 days, and this amount in the second group was 18.59 ± 2.71 days. These differences were meaningful based on Mann-Whitney U test ($P<0.001$; Table 2).

Also, the average days of receiving antibiotics in the first group were 29.21 ± 1.57 and in the second group it was 8.11 ± 2.16 . This difference, based on statistical test of Mann-Whitney U test, was completely meaningful

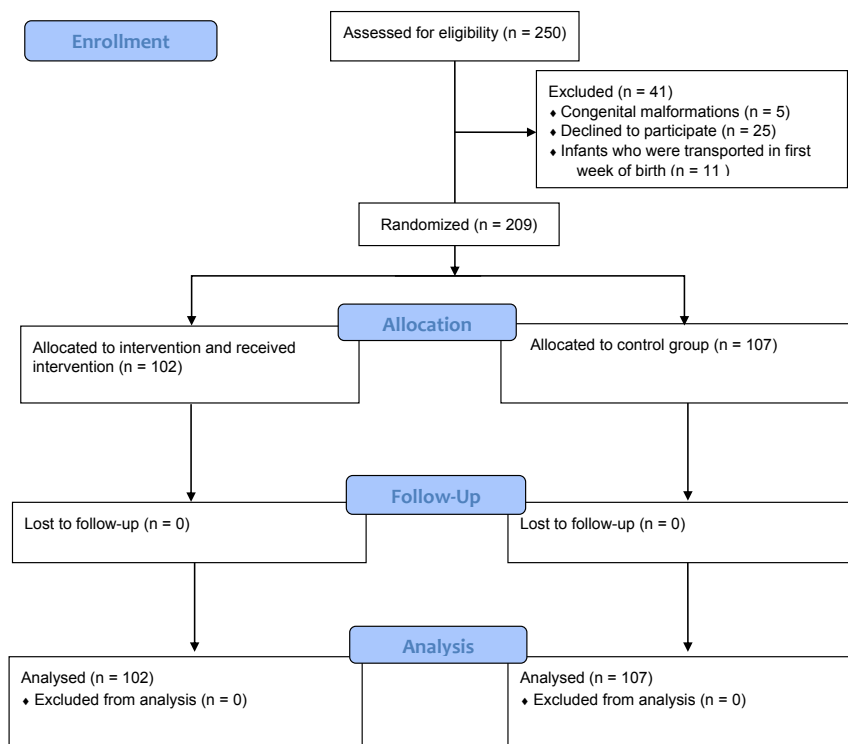


Figure 1. Flowchart of the Study.

Table 1. Demographic Findings in 2 Groups of Very Low Birth Weight Infants With Long-term (>5 Days) and Short-term Empirical Antibiotics Therapy

Variable	Intervention Group n = 102	Control Group n = 107	P
Gender			P=0.08
Male	42 infants, 58.8%	57 infants, 53.3%	
Female	60 infants, 41.2%	50 infants, 46.7%	
Birth weight	1291.52 ± 148.19	1249.2 5± 173.32	P=0.07
Gestational age (wk)	30.21 ± 2.69	29.57 ± 2.09	P=0.06
Apgar score			
1-minute	7.44 ± 0.86	7.02 ± 1.15	P=0.11
5-minute	8.62 ± 0.69	8.40 ± 1.00	P=0.08
No Receiving intravenous feeding	5 (4.9%)	10 (9.3%)	P=0.21
Receiving intravenous feeding	97 (95.1%)	97 (90.7%)	
PROM, yes/they had	12 (11.8%)	21 (19.6%)	P=0.12
Respiratory support			
Mechanical ventilation	0 (0.0%)	40 (37.4%)	P<0.001
CAPA	84 (82.4%)	97 (90.7%)	P=0.16
HFNC	30 (29.4%)	60 (56.1%)	P<0.001
Type of delivery			P=0.14
C section	88 (86.3%)	84 (78.5%)	
Natural childbirth	14 (13.7%)	23 (21.5%)	
Length of stay	18.59 ± 10.88	40.19 ± 20.09	P<0.001
Length of antibiotics therapy	8.11 ± 2.16	29.21 ± 16.19	P<0.001

Abbreviations: PROM, prolong rupture of membrane; CAPA, continues positive airway pressure.

Table 2. Short-term Prognosis in 2 Groups of Very Low Birth Weight Infants With Long-term (>5 Days) and Short-term Empirical Antibiotics Therapy

Variable	Intervention Group n = 102	Control Group n = 107	P
Total days of antibiotics treatment during the hospitalization	8.11 ± 2.16	29.21 ± 16.19	<0.001
Mortality rate	6 (5.9%)	8 (7.5%)	0.65
NEC	9 (8.8%)	11 (10.3%)	0.72
Cerebral hemorrhage	31 (30.4%)	32 (29.9%)	0.93
Chronic lung disease	31 (30.4%)	32 (29.9%)	0.93
Late-onset sepsis	8 (7.8%)	32 (29.9%)	<0.001

Abbreviation: NEC, necrotizing enterocolitis.

($P < 0.001$).

In this observation, in the first group, 27 (25.2%) infants needed a cardiopulmonary resuscitation (CPR) and in the second group this need was for 17 infants. This difference was not found meaningful based on chi-square test ($P = 0.13$; Table 1)

In the first group, 40 infants (37.4%) needed mechanical ventilation. This was different from the infants of the second group, because none of the infants in the second group needed a ventilator. This difference was meaningful based on chi-square statistical test ($P < 0.001$; Table 2).

While 60 infants (56.1%) needed HFNC in the first group, 30 infants (29.4%) needed it in the second group. This difference was also meaningful based on the statistical test of chi-square ($P < 0.001$; Table 1).

In the first group, 52 out of 107 infants (48.6%) needed blood transfusion which was different from that of the second group where this number was 12 infants (11.8%). Based on the chi-square test, this difference is significant ($P < 0.001$; Table 2).

In the first group, 11 infants (10.3%) and in the second group, 9 infants (8.8%) had symptoms of NEC, which this difference was not meaningful based on chi-square test ($P = 0.72$; Table 2).

In the first group, 32 (29.9%) out of 107 infants were marked, and in the second group, 31 (30.4%) out of 102 infants had positive evidences of IVH and bronchopulmonary dysplasia (BPD). This was not significant based on chi-square statistical test ($P = 0.93$).

Discussion

Nowadays there are variable evidences which claim a long-term antibiotic usage causes serious side effects on premature infants (4,5). In our study, we evaluated different variables to see whether there is a need for long-term antibiotics use for premature infants or not. In our study, the duration of hospitalization, the need rate for invasive respiratory support including intubation, need for ventilator, need for prescription of blood products, and the need for HFNC were dramatically decreased in intervention group comparing to control group.

The finding of the current study suggests that there is no meaningful difference between the 2 groups in cases like

death rate, rate of need for resuscitation, rate of urinary tract infection (UTI) and the outbreak of meningitis. Of course, the lack of difference in the rate of urinary tract infection and meningitis shows that long-term antibiotic therapy has no role in preventing invasive and localized diseases. This can fix the concerns regarding probable increase of neonatal infections in infants who despite receiving intravenous serum receive no antibiotics.

In this study, the need for CPAP and parental nutrition were equal in both groups. Also, there was no difference in both groups considering the rate of NEC outbreak.

In 2011, an observation was done by Kuppala et al in which 76 (21%) out of 366 premature infants, who were less than 32 weeks old or had a birth weight less than 1500 g, suffered from late-onset sepsis. Seventeen infants (4.6%) had NEC of second type or higher and 20 infants (5.5%) died (3). However, in our study we did not witness any obvious difference between 2 groups on NEC, but there were side effects comparing to witness group which challenged the long-term usage of empirical antibiotics. In a study conducted by Cotten and colleagues, 23% of the 4039 infants who received antibiotics treatment in the first 3 days of their birth – despite having negative blood culture result – either suffered from NEC or died (2). As we mentioned, in our study the mortality rate in both groups was the same. In a research done by Miall-Allen et al, it was found that CRP factor could be a suitable criterion to stop antibiotic treatment on premature infants, in a way that a negative CRP can limit the usage of antibiotics. In our study, one of the criteria to stop antibiotic treatment was the presence of a negative CRP as well (6).

In a research investigated by Cordero and Ayers, the impact of antibiotics treatment on premature infants and its undesirable side effects were reviewed, and besides mentioning the benefits of this kind of treatment, the weak points were also revealed. Then, it was shown that stopping antibiotics treatment on premature infants who had no sepsis symptoms was a right and secure thing to do (7). In our study, it was shown that despite crucial antibiotics treatment in sepsis cases, its long-term usage can have some side effects. In a research done by Mititilima and Cooke, it was shown that a long-term antibiotic treatment on premature infants with a risk of suspected sepsis,

is not always beneficial and practical (8). Our study approved the results of this study as well. Furthermore, in a research completed by Polin in 2012, it was shown that the use of antibiotic treatment in premature infants with VLBW could increase the risk of NEC and infant mortality rate consequently, if it continued more than 5 days (1). In our study, it was shown that long-term usage of antibiotics creates no difference in mortality rate.

In addition, in the research done by Sivanandan and Soraisham, the results of 96% of the blood cultures after 48 hours of antibiotics treatment on premature infants with birth weight below 1500 g were negative. This rate increased to 98% after 72 hours, which showed a little difference (9). Similarly, in our study the long-term usage of antibiotics on infants with no sepsis did not show any benefit compared to the short-term treatments.

Conclusion

Our study suggests that early stop of antibiotics have no impact on death rate of the infants under study and it does not increase the risk of neonatal infections as well. On the other hand, the use of short-term antibiotics (less than 5 days) on premature infants with VLBW was proved to be effective on decreasing some of the short-term side effects (duration of hospitalization, need for invasive respiratory support, need for the prescription of blood products, and the need for later sepsis work-ups). Before any recommendations for routine use of this policy, it should be assessed in a large group of infants.

Ethical Issues

This study was approved by the ethics committee of Tabriz University of Medical Sciences. We registered this study in Iranian Registry of Clinical Trials (IRCT) database (Registration number: [IRCT201210124113N3](https://www.irct.ir/clinicaltrials/IRCT201210124113N3)).

Conflict of Interests

None to be declared.

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