Is Ceftizoxime an Appropriate Surrogate for Amikacin in Neonatal Sepsis Treatment? A Randomized Clinical Trial

Peymaneh Alizadeh Taheri[1], Hossein Eslamieh[1], and Peyman Salamati[2]

[1] *Department of Pediatrics, Bahrami Hospital, Tehran University of Medical Science, Tehran, Iran*

[2] *Department of Social Medicine, Bahrami Hospital, Tehran University of Medical Science, Tehran, Iran*

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Abstract- Neonatal sepsis, a life-threatening condition, presents with non-specific clinical manifestations and needs immediate empirical antimicrobial therapy. Choosing an appropriate antibiotic regimen covering the most probable pathogens is an important issue. In this study we compared the effectiveness of ceftizoxime and amikacin in the treatment of neonatal sepsis both in combination with ampicillin. In a randomized clinical trial, all term neonates with suspected sepsis referred to Bahrami hospital during March 2008 to March 2010 were evaluated. Patients were randomly recruited into two groups; one group receiving ampicillin and amikacin and the other ampicillin and ceftizoxime. Blood, urine and cerebrospinal fluid cultures, leukocyte count and C-reactive protein level were measured in all neonates. A total of 135 neonates were evaluated, 65 in amikacin group and 70 in ceftizoxime group. 60 neonates (85.7%) in ceftizoxime group and 54 neonates (83.1%) in amikacin group responded to the treatment (P= 0.673 and χ^2 = 0.178). Only 24 (18%) blood samples had a report of positive blood culture. The most frequent pathogen was coagulase negative staphylococcus with the frequency of 58.32% of all positive blood samples. Ceftizoxime in combination with ampicillin is an appropriate antimicrobial regimen for surrogating the combination of ampicillin and amikacin to prevent bacterial resistance against them.

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Introduction

Despite great development in diagnostic and therapeutic procedures, neonatal sepsis still remains a major medical problem with a high morbidity and mortality rate (1-3). It represents for 30-50% of all neonatal deaths in developed countries (4), while afflicting up to 10% of the neonate (5). Sepsis signs and symptoms are non-specific (6) due to the neonate immature immune system making it a lethal clinical condition (7) which necessitates immediate antimicrobial treatment (8). As it is not possible to immediately recognize the etiologic pathogen by culture, it is indispensable to start empirical antibiotic treatment as soon as possible while waiting for the blood culture report to select the most appropriate antibiotic (8). In empirical therapy, proved to reduce neonatal sepsis mortality rate (8, 9), it is endeavored to choose the antimicrobial agents able to cover the very most probable pathogens (10).

Neonatal sepsis is categorized into early and late-onset based on the time of presentation; early-onset neonatal sepsis (EONS), presented in the first 7 days of birth (5), is caused by maternal pathogens transmitted to baby before birth (vertical transmission), during labor or at the time of delivery (8, 9). Late-onset neonatal sepsis (LONS) appears after the first 7 days of birth (5) and caused by nosocomial and community acquired pathogens (8,9).

Choosing the appropriate antibiotic drug for the empirical therapy should be based on the most frequent pathogens and the antimicrobial sensitivity in each hospital (11), because the frequency of pathogens may differ not only between various hospitals (12) but also between various times in a same hospital (13,14).

Combination of Ampicillin and Aminoglycoside or Ampicillin and a third generation of Cephalosporines has been suggested as the drug of choice for neonatal sepsis (15). Thus, the regimens of ampicillin+amikacin

Corresponding Author: Hossein Eslamieh
Department of Pediatrics, Bahrami Hospital , Tehran University of Medical Science, Tehran, Iran
Tel: +98 21 77556969, 913 3510098, Fax: +98 21 77556969, E-mail: eslamyeh@razi.tums.ac.ir

or ampicillin+cefotaxime are the most commonly used antibiotics in our neonatal wards and Neonatal Intensive Care Unit (NICUs) (9). Although aminoglycoside achieves its bactericidal level very soon, it is associated with renal and ear toxicity (16).

Neonatal sepsis must be treated with the first suspicion before determination of the responsible pathogen. Finding a surrogate antibiotic instead of the routine usage of ampicillin + amikacin or ampicillin + cefotaxime is necessary before appearing of bacterial resistance (18).

Several studies about the effectiveness of ceftizoxime in the treatment of neonatal sepsis showed significant results (19,20). Ceftizoxime as a new third generation of cephalosporines has a broad spectrum effect on gram negatives like *E.coli*, *Klebsiella* species, *Proteus mirabills*, *Hemophilus influenza* and Anaerobs. In addition to these effects, it covers streptococcal species, *Staphylococcus aureus* and has a good peneterance in cerebrospinal fluid (20).

As a result, in our study in order to substitute a new combination therapy for sepsis and to prevent appearing of bacterial resistance, we compared the combination of ampicillin and ceftizoxime with ampicillin and amikacin in the treatment of neonatal sepsis.

Materials and Methods

In a single-blind clinical trial, we studied all term neonates hospitalized at Bahrami Hospital, a tertiary center in Tehran, Iran, with probable diagnosis of neonatal sepsis during March 2008 to March 2010. Hospital Ethics Committee approved the study protocol and informed consent was obtained from parents.

According to previous studies, effectiveness of ceftizoxime was reported 90% (19) and that of amikacin 69% (21). The necessary sample size was calculated 39 patients in each group for 80% power; however, we recruited all the neonates appropriate for the study during study period. Simple randomization was used for patient allocation into two groups receiving ampicillin + ceftizoxime or ampicillin + amikacin. The antibiotics doses were as shown in table 1.

All term neonates (>37 weeks) were assessed by a neonatologist for the following, and if positive for any, were included in the study: (1) temperature instability i.e. axillary temperature >38.5 or <36; (2) respiratory distress i.e. mean respiratory rate >60 or hypoxia with PaCO2 <60 mmHg or signs of acute respiratory distress syndrome; (3) poor feeding; (4) poor perfusion i.e. renal output <0.5 cc/kg/hr or metabolic acidosis with pH<7.2 or increased capillary refill >3s; (5) cardiovascular instability i.e. heart rate >160 or decreased blood pressure more than 2 standard deviation below normal for age; (6) decreased neonates movement associated with central cyanosis or any other symptoms or signs suggesting neonatal sepsis. Blood sample was obtained at the beginning for blood culture, complete blood count, C-reactive protein and arterial blood gas analysis.

Culture of cerebrospinal fluid (CSF) and urine were also performed. High risk patients suffering from congenital heart disease, necrotizing enterocolitis, hematologic disorders, neurologic disorders, or respiratory disorders due to meconium aspiration were excluded from the study in order to prevent the effect of resistant sepsis on the results. If neonatal sepsis was ruled out during hospital stay or it was proven to be a nosocomial infection, the patient was excluded from final analysis. Patients were finally categorized as treatment responders and non-responders.

The patient was non-responder if looking ill; worsening in general condition or persistence of initial symptoms and signs along with abnormal laboratory findings after 48 hours, these patients underwent other appropriate antibiotic regimens after being categorized as non-responder.

SPSS 16.0 (SPSS Inc., Chicago, IL) was applied for statistical analysis; Mann-Whitney *U*-test and Chi-square test were used. A $P<0.05$ was considered as statistically significant.

Table 1. Antibiotics and their doses in study groups

Antibiotic	Age < 1 week		Age > 1 week	
Amikacin	10mg/kg/dose	BID	10mg/kg/dose	TDS
Ampicillin	50 mg/kg/dose	TDS	50 mg/kg/dose	TDS
Ceftizoxime	50 mg/kg/dose	BID	50 mg/kg/dose	TDS

Table 2. Demographic characteristics of neonates recruited in the study

	Ampicillin + Ceftizoxime group	Ampicillin + Amikacin group	*P*-value
Mean age	9.4	9.34	0.417
Male/female	1.33	1.4	0.877
Late/early onset	1.12	0.8	0.338

Results

During 2 years of study period, 170 term neonates were admitted at our center with clinical manifestations comparable with neonatal sepsis, among which 35 were excluded due to previously mentioned exclusion criteria. Demographic data are provided in table 2. Considering all the patients, 46% presented with EONS and 54% with LONS. Number of patients recognized as treatment responders was 60 (85.7%) and 54 (83.1%) in ampicillin + ceftizoxime group and ampicillin + amikacin group, respectively. Chi-square test resulted in a *P*-value = 0.673 and χ^2 = 0.178, which indicated no significant difference among the two groups. Only 24 (18%) blood samples out of 135 resulted in a positive blood culture; 13 samples in ampicillin + ceftizoxime group and 11 samples in ampicillin + amikacin group. Mean age of patients with positive blood culture was 9 ± 2. The most common isolated microorganism was coagulase-negative staphylococcus in both groups. All the reported bacteria are listed in table 3.

Discussion

According to our knowledge, our study was the first clinical trial comparing the effectiveness of ampicillin+ceftizoxim with ampicillin + amikacin in the treatment of neonatal sepsis.

Our study did not show any significant difference between the effectiveness of the two pairs of antibiotics. However 86% of the neonates who underwent antibiotic therapy by ceftizoxime responded to the treatment and only 14% were non-responders who underwent other antibiotic regimens.

Yamauchi *et al.*, in a study on the effectiveness of ceftizoxime in the treatment of neonatal sepsis, reported an effectiveness of 90% for the drug (19). In another study ceftizoxime was reported to be effective in 87.5% of the patients; our results were comparable with both studies (20). Efficacy of combination therapy with ampicillin + amikacin in treatment of neonatal sepsis was reported to differ between 61% for E. coli to 100% for Serratia, with a mean of 70% for neonatal sepsis generally (22). A study from Kashan province (Iran) showed a comparable efficacy of 69%for combination of ampicillin and amikacin (21). Our study resulted in 83% efficacy for the combination which was more than previous studies.

EONS and LONS respectively afflicted 46% and 54% of the neonates in our study. In a study in a hospital in Urmieh (Iran), it is reported that EONS was more frequent than LONS (5). Also some reports from other parts of Iran as well as India and Pakistan stated EONS to be more frequent than LONS (13, 23-26). In our study this difference is probably related to this fact that our hospital is not a maternal hospital and is a referral center.

Culture-proved sepsis was present in only 18% of the neonates; however in a study by Clark *et al.,* 2% of the neonates had a positive blood culture (11) and Gheibi *et al.,* showed it to be 11% (5).

Coagulase negative *Staphylococcus* (CoNS) was the most frequent bacteria among positive blood cultures representing for 58.32% of all culture-proved sepsis and *Staphylococcus aureus* and group B *Streptococcus* (GBS) were the next with 16.67% for each. *E.coli* and Enterobacter were either responsible for one neonatal sepsis in our study. In the study by Gheibi et al in Urmieh, CoNS (54.6%), *S. aureus* (6.6%) and GBS (0.9%) were the most common causes of neonatal sepsis (5).

Table 3. Isolated bacteria from blood samples of the patients.

Bacteria	Ampicillin + Ceftizoxime group	Ampicillin + Amikacin group	Study population
Coagulase-negative *Staphylococcus*	8 (62%)	6 (54.54%)	14 (58.32%)
Staphylococcus aureus	2 (15%)	2 (18.16%)	4 (16.67%)
Group B Streptococi	3 (23%)	1 (9.1%)	4 (16.67%)
E.coli	-	1 (9.1%)	1 (4.17%)
Enterobacter	-	1 (9.1%)	1 (4.17%)

In another study CoNS was the etiologic pathogen of about 22% of EONS and approximately half of LONS (8). Kaplan *et al.,* reported CoNS, *Enterococcus* and *S. aureus* with the frequency of 38%, 11.2% and 9.3% respectively as the common causes of neonatal sepsis in the study (27). Several studies indicated that CoNS positive blood cultures were often considered as contamination and were excluded from analyses (28, 29). Another study stated that CoNS isolated from blood cultures of LONS were not a significant cause of neonatal death and therefore did not need any empirical antimicrobial therapy (30). Besides, in another study it is mentioned that if CoNS was presented in more than half of the positive blood cultures of LONS, it is considered as true infection not contamination (31). Although in our study CoNS was responsible for 58.32% of the positive blood cultures, future studies should evaluate either it was a contamination from the laboratory staff or equipments or a true infection from the patients' blood samples. According to increasing frequency of CoNS positive neonatal sepsis reported by other authors and based on the other study in Iran reporting CoNS as the most frequent cause of neonatal sepsis, CoNS positive blood cultures in our study seems more probable to be true infection.

Clark *et al*., found that the mortality rate in neonates underwent treatment with ampicillin + cefotaxime was higher than those receiving ampicillin + gentamycin concluding that using the combination of ampicillin and cefotaxime in the first 3 days of birth might increase the risk of neonatal death (11). As ceftizoxime and cefotaxime are both a third generation cephalosporin, it is considerable that the concurrent use of ampicillin and ceftizoxime may also increase the risk of neonatal death. On the other hand several studies have shown the effectiveness of ceftizoxime in neonatal sepsis (19,20). Although in our study none of the neonates in neither groups expired, studies should mention this important point beside using a larger sample size. In conclusion, the present study showed that the combination of ampicillin and ceftizoxime can be an appropriate surrogate for the antimicrobial regimen of ampicillin and amikacin in the treatment of neonatal sepsis; however, it is recommended that future studies consider short- and long-term side effects while comparing the two regimens.

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