Comparative Study in Neonates with Septicemia Using Meropenem Versus Ceftriaxone Plus Vancomycin.

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ABSTRACT:

BACKGROUND:

Neonatal septicemia is an important cause of mortality in both developed and developing countries . The type and pattern of organisms that cause neonatal sepsis changes over time. In addition the causative organisms have developed increased drug resistance for the last two decades .

OBJECTIVE:

To compare the effectiveness and tolerability of two different antibiotic regimens in the initial treatment of suspected neonatal septicemia.

PATIENTS AND METHODS:

This is a controlled clinical trial on 80 neonates with a presumptive diagnosis of septicemia who were admitted to the children welfare teaching hospital of Baghdad from August 2010 to March 2011.Both early onset sepsis and late onset sepsis were included in this study. The diagnosis of probable sepsis was based on the presence of a repertoire of clinical symptoms and signs . Initial tests performed included complete blood count , CRP, and blood cultures. Neonates were randomly divided into two groups of forty neonates per each. The first group was given meropenem of 30mg/kg /dose every 12 hours , while the second group was treated by a combination of ceftriaxone 50mg/kg/dose every 12 hours plus vancomycin of 15mg/kg/dose every 12 hours. The duration of treatment was 7-14 days.

RESULTS :

The patients variables in the two treatment groups at entry were comparable. The most prevalent clinical features were reluctance to feed (83.75%), lethargy(70%) , pallor (47.5%), irritability (38.75%), and hypothermia(32.5%).Of the 80 neonates , 81.25% had positive CRP , 58.75% had abnormal WBC count(<5000 /mm^3 or > 20000/mm^3) , and 48.75% had positive blood culture for bacteria .Staphylococcus coagulase negative accounted for28.2% of the total isolates followed by E coli (23%) , Klebsiella pneumonia (20.5%), pseudomonas aeruginosa (17.9%), streptococcus (7.7%), and staphylococcus aureus (2.5%). The overall responses to treatment was significantly higher $P<0.05$ in the meropenem group with a cure rate of 87.5 % versus 67.5 % in vancomycin plus ceftriaxone . Neonates with early onset sepsis showed a significantly higher success rate ($p<0.05$) with meropenem than with ceftriaxone plus vancomycin (the cure rate 93.1% versus 60%)While there were no differences between the two treatment group regarding late onset sepsis 72.2 % versus 80 %.

CONCLUSION:

The most effective antibiotic for early onset sepsis in this study was meropenem, while it had equal effectiveness with the combination of ceftriaxone plus vancomycin against late onset sepsis.

KEY WORDS : septicemia , meropenem versus ceftriaxone plus vancomycin

INTRODUCTION:

Neonatal sepsis remains an important cause of morbidity and mortality among neonates in developing countries accounting for 30-50% of total deaths each year [(1)].Unfortunately there are no specific signs and symptoms of neonatal sepsis and the onset and course of progression are much faster than in older children[(2)].Neonatal sepsis has been classified as either early onset sepsis (0-7 day of age) or late onset sepsis (7-28 days of age)[(3, 4)]. Early onset sepsis is mainly due to bacteria acquired before and during delivery , and late onset sepsis acquired after delivery (nosocomial or community sources) but it may occur via vertical transmission at birth , leading

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to colonization and later to infection [5]. The most common route of early onset sepsis in preterm and term neonates is via ascending amniotic infection. Members of the maternal genital flora , such as Group B Streptococcus (GBS) and Escherichia coli (E coli) , the organisms responsible for the majority of cases of early onset sepsis , may ascend through the birth canal to the amniotic fluid either through intact amniotic membranes or, more commonly , after the rupture of membranes [6].While in late onset sepsis , organisms may enter the blood stream through breaks in the skin or mucosa or by gastrointestinal translocation or may be introduced through invasive devices such as vascular catheters , endotracheal tubes , or feeding tubes. Alternatively , nosocomial infection may result from infusion of contaminated intravenous solutions or from contaminated milk formula (7).

Management of the newborn with sepsis consists essentially of appropriate antibiotic therapy and supportive care. The choice of antibiotic therapy is best guided by the knowledge of the aetiologic agent. This however, is usually not immediately possible. Thus , it is customary to initiate treatment with an empiric choice of antibiotic(s)[8].

Empiric antibiotic treatment varies between neonatal intensive care units and countries and there are currently no consensus on the choice of empiric antibiotics[9], however, The mainstay of empiric therapy for early onset sepsis for both term and preterm infants in most centers is ampicillin and gentamicin, pending blood culture results. However , resistance to these antimicrobials agents is emerging and continues to be an important problem worldwide [8,10] .While for empiric treatment of suspected late onset sepsis, nafcillin or oxacillin and an aminoglycoside may provide sufficient initial coverage , however , most coagulase negative staphylococcus are resistant to beta-lactam antibiotics and so that many centers use empiric vancomycin for late onset sepsis[10,11].Moreover when choosing treatment for late onset sepsis , consideration should also be given to the possibility of Pseudomonas and anaerobic bacteria especially in neonates with intestinal perforation[12].

Third generation cephalosporins are increasingly being used or considered for treatment of neonatal sepsis[13] .However , disadvantages associated with cephalosporins include ineffectiveness against enterococci and Listria monocytogenes and the concerns over the rapid development of resistance[14]

Recently , a new broad spectrum carbapenem , has been under investigation on a world – wide basis for the treatment of moderate to severe infections[15]. It has been reported to have an ultra broad spectrum activity against microorganisms , including most of the major aerobic (gram – negative and gram-positive) and anaerobic pathogens and have good penetration into body fluids and tissues[16]. When meropenem was compared with numerous multiple –drug regimens consisting of second and third generation cephalosporins, aminoglycosides, clindamycin , ciprofloxacin , and or metronidazole ; meropenem demonstrated broader spectrum of activity and generally found to be more potent[17]

Aim of the study: This study is aimed at investigating the efficacy and tolerability of meropenem in the treatment of neonatal septicemia in comparison to a combination of vancomycin plus ceftriaxone .

PATIENTS AND METHODS :

This was a controlled , randomized trial conducted between August 2010 to March 2011 , included a total of 80 neonates with a presumptive diagnosis of septic who were admitted to the children welfare teaching hospital of Baghdad. .The approval of the protocol was obtained from the Institutional Review Board (IRB) of the hospital.. Written consent was obtained from each of the caregivers of the participants of each group prior to the start of the study.

Both early onset sepsis (disease occurring in less than 7 days of age) and late onset sepsis (disease occurring in more than 7days of age) were included in this study.

The diagnosis of probable sepsis was based on the presence of a repertoire of clinical symptoms and signs .

Neonates were randomly divided into two treatment groups. The first group received meropenem of 30mg/kg /dose every 12 hours , while the second group was treated by a combination of ceftriaxone 50mg/kg/dose twice daily plus vancomycin of 15mg/kg/dose twice daily.

Exclusion criteria (neonates that were excluded from the study) included ; neonates with major congenital malformations , severe birth asphyxia

meningitis , those who were already on antibiotics , and those undergoing surgery .

Identification ,demographic data and clinical details of the sepsis episode and laboratory results were recorded in structured case report form.

Initial tests performed included complete blood count (CBC), C- reactive protein (CRP) , and blood cultures.

Other investigations were done when clinically indicated including spinal fluid microscopy , liver function tests, complete blood count , and chest or abdominal radiographs.

The antimicrobial therapy continued for 7-14 days. If there was no satisfactory response at the time of culture result, then the neonate was shifted to the most appropriate drug according to the culture sensitivity test.

Clinical response was defined as satisfactory if patients were cured (complete remission of systemic or local signs and symptoms of infection without the addition of other antibiotics) ,while failure of treatment was defined as the demonstration of no improvement or deterioration of signs and symptoms.

Supportive care was provided in a similar fashion to neonates in both groups as per unit guidelines. The use of breast milk is aggressively promoted in our unit .

Blood culture:

The gold standard for diagnosing neonatal sepsis remains the blood culture that should be performed in all cases of suspected sepsis prior to starting antibiotics , even though , in many cases , blood cultures are negative in the face of strong clinical indicators of septicemia .

Using aseptic technique by applying povidone iodine at the site of vein puncture ,the skin should be allowed to dry for at least 1 minute before the sample is collected. Three milliliters of venous blood was drawn from the antecubital or femoral vein. One ml was inoculated directly into brain heart infusion broth and transported to the laboratory for incubation and subsequent processing.

All blood cultures were incubated aerobically at 37C and inspected daily for 7days for the presence of visible microbial growth by observing any of the following : turbidity , hemolysis , gas production , coagulation of broth. For blood cultures that showed signs of microbial growth , subcultures were made onto blood , chocolate and macConkey agar. All positive blood cultures were identified by their characteristic appearance on their respective media, gram staining reaction and confirmed by the pattern of biochemical reactions using the standard method[18].

Blood culture broth which showed no microbial growth within 7 days was reported as culture negative , only after result of routine subculture on blood , macConkey and chocolate agar.

Finally , antimicrobial susceptibility of all isolates was determined by disk diffusion method according to the criteria of the National Committee for Clinical Laboratory Standard (NCCLs) [18].

C-reactive protein(CRP) test

The remaining 2ml blood was used for CBC as well as measurement of CRP.

Positive CRP was defined as presence of agglutination at a dilution of $\geq$ 1:2 by latex agglutination test, which corresponded to a CRP titer of $\geq$ 12mg/L.

Statistical analysis:

Data analysis was done using SPSS version computer 15 software . comparisons were made using Chi-square test with Fisher exact tests. A p- value of < 0.05 was considered indicative of a statistically significant difference.

RESULTS :

A total of 80 admitted neonates (0-28 days of age) with suspected cases of sepsis were investigated .The demographic data of neonates in both treatment groups were comparable and are presented in table 1.

Risk factors associated with neonatal sepsis included low body weight 53.75% , maternal fever 31.25% , maternal urinary tract infection 31.25% , premature rupture of membrane 23.75% .

The clinical features of early onset and late onset sepsis are summarized in table 2 . The most prevalent clinical features were reluctance to feed (83.75%), lethargy(70%) , pallor (47.5%), irritability (38.75%), and hypothermia(32.5%).

Laboratory finding

Among the 80 neonates admitted with suspected cases of sepsis , 81.25% had positive CRP , 48.75% had positive blood culture for bacteria , and 58.75% had abnormal WBC count(<5000 /mm^3 or $>$ 20000/mm^3) as depicted in table 3.

The types of organisms isolated and their sensitivity in both treatment groups are shown in table 4 , Staphylococcus coagulase negative accounted for 28.2% of the total isolates followed by E coli (23%) , Klebsiella pneumonia (20.5%), pseudomonas aeruginosa(17.9%),

streptococcus(7.7%), and staphylococcus aureus (2.5%).

Overall response to treatment in both groups is shown in table 5 and was significantly higher P<0.05 in the meropenem group with a cure rate of 87.5 % versus 67.5 % in vancomycin plus ceftriaxone .Neonates with early onset sepsis showed a significantly higher success rate (p<0.05) with meropenem than with ceftriaxone plus vancomycin (the cure rate 93.1% versus 60%)while there were no differences between the two treatment group regarding late onset sepsis 72.2 % versus 80 %.

The overall incidence of side effects in both treatment groups was low (6.5%).All side effects were minor but occurred more frequently with the combination treatment group. The most frequently reported adverse effects were mild diarrhea and a mild rash.

Evaluation of the treatment response according to CRP was shown in table 7, there was a significant decline in the CRP positivity in the both groups after 3 and 7 days of treatment.

Table 1:Demographic data of neonates at entry

Presentation	Meropenem	Ceftriaxone plus vancomycin	P value
Number of neonates	40	40	
Term Preterm	9 31	12 28	0.3 0.3
Onset Early Late	 29 11	 25 15	 0.2 0.2
Body weight <2kg 2-3kg >3kg	 23 12 5	 19 15 6	 0.3 0.3 0.5
Mode of delivery NVD C/S	 25 15	 26 14	 0.5 0.5
Perinatal maternal history Maternal fever Maternal UTI PROM > 12hr	 11 16 11	 14 9 8	 0.3 0.1 0.3

- PROM : Premature rupture of membranes
- NVD : Normal vaginal delivery
- C/S: Caesarian section
- UTI : Urinary tract infection

Table 2 : Clinical features at presentation

Clinical findings	Meropenem	Ceftriaxone + vancomycin	P value
General			
Sclerema	2	3	0.5
Pallor	15	23	0.1
Jaundice	12	8	0.3
Temperature			
Fever (> 37.5c°)	7	11	0.2
Hypothermia(<35 c°)	16	10	0.1
Euthermia (36.5-37.5 c°)	17	19	0.4
Respiratory			
Apnea	4	3	0.5
Tachypnea	5	4	0.5
Cyanosis	8	10	0.4
Respiratory distress	2	4	0.3
Reluctance to feeding	35	32	0.3
Neurological			
Lethargy	29	27	0.3
Irritability	16	15	0.5
Fit	4	2	0.3
Absence of Moro reflex	7	5	0.4
GIT			
Diarrhea	3	5	0.4
Vomiting	5	7	0.4
Malena	2	1	0.5
Abdominal distention	5	3	0.4
Hepatomegaly	3	3	1
Splenomegaly	3	2	0.5

Table 3: Laboratory finding at presentation.

Parameter	Meropenem	Ceftriaxone plus vancomycin	P value
CRP +ve	34	31	0.3
Blood culture +ve	21	18	0.3
WBC count			
Low	11	10	0.5
High	15	11	0.2
Normal	14	19	0.3

Table 4: Types of organism isolated and their sensitivity in both treatment groups

Type of bacteria	Meropenem in culture +ve neonates		Ceftriaxone plus Vancomycin in culture +ve neonates		P value
	Sensitive	Resistant	Sensitive	Resistant	
E. Coli	5	0	3	1	0.4
Pseudomonas aeruginosa	3	1	1	2	0.3
Staph.Coagulase negative	5	1	4	1	0.6
Klebsiella pneumonia	3	1	3	1	0.6
Streptococcus group B	1	0	1	1	0.7
Staph. aureus	1	0	0	0	1

Table 5: Overall response to treatment

Treated groups	Meropenem	Ceftriaxone plus vancomycin
Cured	35/40 (87.5 %)*	27/40(67.5 %)
Antibiotic changed according to culture sensitivity tests	3/40(7.5%)	7/40(17.5%)
Mortality	2/40(5%)	6/40(15%)

- $p < 0.05$

Table 6:Early onset versus late onset sepsis response to treatment .

	Early onset		Late onset	
Drugs	Success	Failure	Success	Failure
Meropenem	27(93.1%)	2	8(72.7%)	3
Vancomycin + ceftriaxone	15(60%)	10	12(80%)	3
P value	0.004		0.3	

Table 7 : Evaluation of the treatment response according to CRP

Treated groups	Positive CRP At initial presentation	Positive CRP After 3 days of treatment	Positive CRP after 7 days of treatment
Meropenem	34/40	12	2
Ceftriaxone plus Vancomycin	31/40	16	3

DISCUSSION:

The present study is undertaken to evaluate the response of empiric therapy with meropenem or a combination of ceftriaxone plus vancomycin in neonatal sepsis , and to identify the pattern of bacterial isolates encountered. Moreover an attempt was also made to identify the possible risk factors responsible for neonatal septicemia. Risk factors associated with neonatal sepsis include low body weight 53.75% , maternal fever 31.25% , maternal urinary tract infection 31.25% , premature rupture of membrane 23.75% , which is comparable with the reports from other developing countries e.g. India[19] and Ethiopia [20].

In the present investigation , 67.5% and 32.5% neonates presented with early onset sepsis and late onset sepsis respectively .We found that early onset sepsis was more common than late onset sepsis , which is in agreement with the reports from other developing countries e.g. in Bangladesh (70.7 % vs 29.3%) [21], in Ethiopia (98.7% vs 1.3%) [20], and Iran (77.5% vs 22.5%) [22].

The clinical features of sepsis in the present study are also similar to those reported by other studies [20, 21] .

Blood culture to isolate the offending pathogen remains the mainstay of diagnosis for neonatal sepsis . The results of blood culture may take about 4 days , necessitating initial empirical treatment of suspected sepsis. In this study out of 80 neonates admitted with suspected cases of sepsis , 48.75% were positive for bacterial culture. The isolation rate of bacteria in this study is comparable to rates reported in Nigeria (45.9%) [23] , India (52.6%) [24], and Pakistan (54%) [25].

Blood cultures may be negative in the face of strong clinical indicators of septicemia ; maternal antibiotics given in the majority of preterm deliveries may suppress the growth of bacteria in culture [20]. False –negative blood cultures in apparently septic neonates may also result from insufficient sample size[26] ; technical difficulties associated with phlebotomy in small , sick preterm neonates often limit the volume of blood obtained and thus decrease the sensitivity of blood culture for diagnosing sepsis in this population.

Regarding the frequency of isolation of gram positive and negative bacteria from blood culture in this study was 39.4% VS 60.6% , respectively which show that gram negative bacteria were responsible for most cases of neonatal sepsis. This finding is comparable to the results reported by Aftab et al 42% VS 58% [25] , Simiyu et al 33.4% VS 66.6% [27] , and Aqnihotri et al 41.5% % VS 58.5 [28] .

In the present study, staph coagulase negative was the most common isolate (28.9%) ,followed by E coli (23.7%) , Klebsiella pneumonia (21%) , pseudomonas aeruginosa (18.4%), streptococcus group B (7.9%) , and staph aureus (2.6%).The pattern of isolated organisms in our study slightly differs from the findings in Iran [22], India [29] ,and Jamaica [30], where pseudomonas aeruginosa was the most common cause of neonatal sepsis followed by Klebsiella spp , and E coli .

In the present study among the 80 neonates admitted with suspected cases of sepsis , 81.25% had positive CRP and there was a significant decline in the CRP positivity in both groups after 3 and 7 days of treatment.

Regarding the response to treatment, although the bactericidal activity of meropenem was

similar to that of ceftriaxone plus vancomycin [31]. However in present study meropenem was significantly ($p< 0.05$)more effective than the combination of ceftriaxone plus vancomycin in treatment of early onset sepsis (93.1%vs 60%)respectively which is in accordance with Gaza study[32] while there was no significant difference in the cure rates between two treatment groups in late onset sepsis (72.7%vs 80%) respectively .Moreover , the results of present study are compatible with Nilgun et al [16] observations which showed that overall clinical and bacterial response was better in the newborns treated with meropenem than those treated by ampicillin , cefotaxime , ceftriaxone and aminoglycosides.

Meropenem was better tolerated than the combination of ceftriaxone plus vancomycin. However the total incidence of drug-related adverse events in combination treatment group was low. The most frequently reported adverse effects with these medications were mild diarrhea and a mild rash.

CONCLUSION:

The most effective antibiotic for early onset sepsis in this study was meropenem, while it had equal effectiveness with the combination of ceftriaxone plus vancomycin against late onset sepsis.

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