NEONATAL SEPTICEMIA: A REAPPRAISAL WITH SPECIAL REFERENCE TO THE USE OF CEFOTAXIME

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ABSTRACT

In a study period of one year, 381 babies (38.7% of all nursery admissions) were clinically diagnosed to have sepsis. Of these, 156 (40.9%) had positive blood cultures. Klebsiella was by far the commonest organism isolated (41%) followed by other Gram negative organisms. Gram positive organisms were uncommon (8%). Sensitivity of Gram negative organisms was poor to penicillin (11%) and ampicillin (18%); significantly better to kanamycin (65%), gentamicin (74%) and best to cefotaxime (79%). Only 8% isolates were resistant to all antibiotics. Combination of cefotaxime and gentamicin was effective against 90% of the isolates (in vitro) as compared to 74% for gentamicin and ampicillin. In vivo, mortality in the cefotaxime treated group was significantly lower (24.3%) than control group (47%) although both groups were clinically and bacteriologically comparable ($p < 0.05$).

Key words: *Neonatal septicemia, Antibiotics, Cefotaxime.*

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Inspite of improved understanding in its causation and presentation, septicemia remains the leading cause of neonatal mortality and morbidity(1-4). Inadequate standards of asepsis, contaminated equipment and hospital cross-infection make the small ill baby in a neonatal nursery particularly susceptible. Changing bacteriological patterns(5-7) and ever emerging resistance necessitate the continuous development of newer and more effective antibiotics. Amongst newer antibiotics, cefotaxime (CTX) has been claimed to be especially suitable for neonates(8-10). However, in order to forestall the indiscriminate use of this drug, it is necessary to appraise ourselves of the current incidence, bacteriological profile, sensitivity patterns and outcome of sepsis in relation to the antibiotics available.

Materials and Methods

This study was conducted at the Neonatal Unit of K.E.M. Hospital, Pune. This 24 bedded unit, offering Level II-III facilities, caters to approximately 1000 high risk neonates annually. Nearly 60% of these babies are referred from other hospitals in Pune and surrounding areas. Babies with frank sepsis(11) are not admitted. All babies who were clinically suspected to have developed sepsis during their nursery stay, were screened by a septic and bacteriological work up. Final diagnosis of septicemia was made as per Singh *et al.*(7).

While awaiting bacteriological diagnosis, a combination of intravenous ampicillin and gentamicin in appropriate doses was initiated. During the year of study, intravenous cefotaxime (CTX) was added (alone or in combination), when available, (*a*) in case of failure of clinical response of previous antibiotic regimen; and/or (*b*) superior

sensitivity of the isolated organism to cefotaxime(12). In newborns with pyogenic meningitis and in those with severe surgical sepsis (necrotising enterocolitis, intestinal obstruction, peritonits), CTX was used as a primary drug, whenever available, in combination with intravenous ampicillin.

The group of babies who received cefotaxime (CTX group) was compared with respect to outcome with the group of babies for whom cefotaxime was either not available or not indicated (control group).

Tolerance and side effects of CTX was also monitored by the following studies before, during and after therapy: (*i*) Hematological parameters (total leucocyte count, eosinophil count); (*ii*) Urine examination (albumin, sugar, microscopy); and (*iii*) Biochemical parameters (SGPT, SGOT, blood urea, creatinine).

All data was fed to an IBM PC/XT Computer and analysed by software programmes. Chi square test was used for determination of statistical significance.

Results

In a study of one year, 982 high risk newborns were admitted to the neonatal unit. During the nursery stay, 381 (38.7%) were clinically diagnosed to have sepsis. One hundred and fifty six (40.9%) of these of 15.8% of all admissions had bacteriologically positive blood cultures. Further analysis is restricted to these 156 babies and presented as *in vivo* and *in vitro* studies.

In Vitro Studies

The organisms isolated from blood cultures of 156 babies with their sensitivity pattern to commonly used antibiotics is seen in *Table I*. Klebsiella was by far the commonest organism isolated(41%) followed by *E. coli*, *Pseudomonas, Acinetobacter* and *Proteus*. Gram positive organisms were uncommon (8%). Sensitivity of Gram negative organisms was poor to penicillin (11%) and ampicillin (18%); significantly better to Kanamycin (65%), gentamicin (74%) and best to Cefotaxime (79%). In 5% cultures, cefotaxime sensitivity was not done due to non-availability of sensitivity discs. The superior sensitivity of cefotaxime over gentamicin however, did not reach statistically significant proportions, except specifically for *Proteus* and *Acinetobacter* ($p<0.05$).

Twenty five (16%) of all isolates were resistant to CTX (Cefotaxime) and 12 (8%) were resistant to all antibiotics tested. Combination of CTX and gentamicin was effective against 90% of the isolates (*in vitro*) as compared to 74% for gentamicin plus ampicillin ($p<0.01$).

In Vivo Studies

Forty nine of the 156 babies with positive blood cultures died before 48 hours of starting antibiotic therapy and hence are excluded from further analysis. Sixty six of the remained received a combination of ampicillin plus gentamicin (control group) whereas 41 received CTX with or without other antibiotics (CTX group).

Both groups were clinically and bacteriologically comparable (*Table II*). However, the mortality in the CTX group was significantly lower (24.3%) than the control group (47%) ($p<0.05$). Further, the outcome in the CTX group was seen to be related to the degree of sensitivity of the organism to the antibiotic (*Fig*). Correlating the organisms cultured with outcome, it was found that mortality was highest for *Proteus* (83%), intermediate for the other

TABLE I—*Blood Cultures and Antibiotic Sensitivity Pattern*

Organisms	*Kleb*	*E. coli*	*Pseudo-monas*	*Acineto-bacter*	*Entero-bacter*	*Salmo-nella*	*Proteus*	*Staph. albus*	*Staph. aureus*	*β haem strep*
n	64	19	19	16	8	6	12	4	4	4
(%)	(41)	(12.1)	(12.1)	(10.2)	(5.1)	(3.8)	(7.7)	(2.5)	(2.5)	(2.5)
% sensitive to Penicillin	7	13	11	31	14	0	0	83	50	100
Ampicillin	7	27	17	54	43	0	11	83	50	75
Kanamycin	80	100	37	38	71	0	33	67	50	0
Gentamicin	88	93	63	54	86	60	11	83	100	25
Cefotaxime	78	80	58	92	80	80	100	33	100	50

TABLE II—*Comparison of CTX and Control Groups*

Group	Control group	CTX group
Mean birthweight (kg)	1.66±0.47	1.7±0.5
(Range)	(0.74 - 3.0)	(1.0 - 3.0)
Male : Female ratio	1.3 : 1	1.6 : 1
Mean gestational age (weeks)	35.3±3.73	35.5±3.54
(Range)	(28-40)	(28-40)
Associated problems (n)		
Pyogenic meningitis	2	3
Pnuemonia	0	3
Hyperbilirubinemia	6	2
Hyaline membrane disease	2	1
Hypoxic ischaemic encephalopathy	4	4
Meconium aspiration	2	1
Gastroenteritis	0	6
Infant of diabetic mother	1	1
Intracranial bleed	3	2
Surgical sepsis	5	4
Mortality (%)*	47	24.3

Chi-square 4.54; $p < 0.05$.

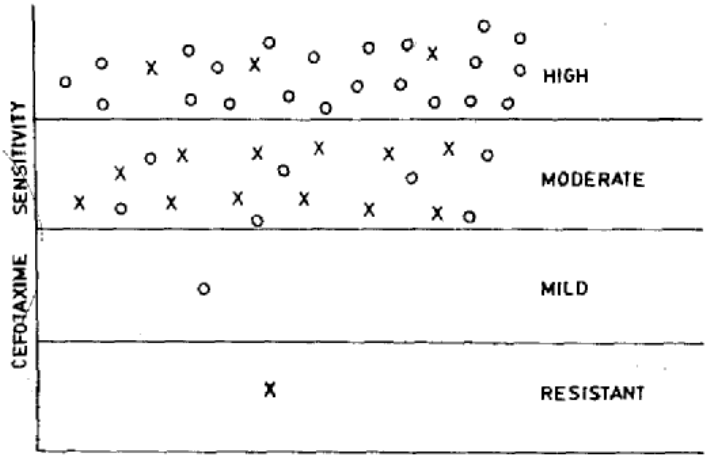

Fig. Cefotaxime: Sensitivity Related Outcome ×=*Dead,* o=*Alive. Cefotaxime sensitivity—zone size interpretative standards(12): Resistant R, Mild sensitivity 1 +, Moderate sensitivity 2+, High sensitivity 3+/4+*

Gram-negative organisms (33-54%), and least for Gram-positive organisms (0-25%).

Local thrombophlebitis was seen in 14 (29%) of babies receiving CTX. Three developed cutaneous gangrene and one an abscess at the intravenous site. Further, one baby developed thrombocytopenia, one cholestasis and one each a transient rise of SGPT and blood urea. None of these problems, however, were significantly greater than the control group.

Discussion

It has been estimated that about 10 per 1000 of all live births demonstrate clinical evidence of neonatal septicemia(2). The incidence is understandably much higher in neonatal nurseries, where as many as 25-40% of all admissions may be affected(5,13). However, baceriological diagnosis is not always possible and

depending on the facilities available, upto 60% of clinically suspected cases have positive blood cultures(5,13-15).

Nearly 15.8% of all admissions and 40.9% of clinically suspected septic babies in our high risk nursery had positive blood cultures. Klebsiella was the commonest organism isolated (*Table I*), followed by other Gram negative organisms. This pattern is similar to other Indian contemporary studies(2,5). Bacteriological patterns in neonatal septicemia have infact changed over the years in India as in the West(6) obviously reflecting aseptic precautions, instrumentation and emergence of antibiotic resistance. *Staphylococci* and *Pseudomonas*, tyrants of nursery epidemics in the seventies no longer appear dangerous in comparison to *Klebsiella*. Interestingly, β-hemolytic *streptococcus* of great concern in the West(16-18) does not seem to have established a foothold in Indian nurseries as yet.

One of the most disconcerting findings of our study as in other recent studies(5,11), is the widespread emergence of bacterial resistance to commonly used antibiotics. Not more than 25% of the Gram negative organisms cultured were sensitive to penicillin and ampicillin and these drugs should perhaps no longer be used as first line antibiotics for neonatal septicemia. On the other hand, inspite of its wide and rather indiscriminate use, gentamicin still appears to be effective against upto 75% of organisms. The superior sensitivity of third generation cephalosporins, in particular, cefotaxime has been demonstrated by Gupta *et al.*(21) and a number of other Western studies(8,9,19,20). However, more than 15% of our isolates were resistant to cefotaxime and hence this drug too, if used as a primary antibiotic should be combined with another, such as gentamicin. In fact, the susceptibility of organisms to a combination of gentamicin and cefotaxime was 90% as against 74% for gentamicin alone and 79% cefotaxime alone.

Pharmacologically, cefotaxime appears to be ideally suited for neonatal septicaemia in view of its high and broad spectrum antibiotic activity, its ability to cross the blood brain barriers, its β-lactamase resistance and remarkable tolerance(10). However, the drug is expensive (sometimes prohibitively) and in view of its emerging resistance should, at present be reserved for severe life threatening infections or in cases where bacterial cultures are resistant to all other available drugs.

In conclusion, septicemia remains one of the commonest problems in the nursery. Bacteriological diagnosis is not always possible. Mortality is high, 30% dying within 48 hours of diagnosis. Cefotaxime plus gentamicin proved the most effective combination of antibiotics both *in vitro* and *in vivo*. Resistance to cefotaxime is being increasingly encountered and the drug must, therefore, be spared for serious infections only.

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