Original Articles

EVALUATION OF RISK FACTORS FOR FATAL NEONATAL SEPSIS

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Objective: *To evaluate risk factors for fatal neonatal sepsis.* ***Design:*** *Prospective study.* ***Setting:*** *Referral neonatal unit of a teaching hospital.* ***Subjects:*** *171 neonates admitted with sepsis.* ***Methods:*** *Clinical examination and investigations on the day of admission were recorded and the neonates followed up to determine the final outcome.* ***Results:*** *The overall fatality was 48.5%. In the univariate analysis, the factors significantly associated with death were weight, gestational age, age at onset of sepsis, hypothermia, requirement of lPPV, presence of refractory septic shock, neutropenia, metabolic acidosis and raised prothrombin time. However, in the multivariate analysis, only neutropenia, metabolic acidosis, increased prothrombin time and refractory septic shock retained their, significance. The adjusted odd's ratio (95% confidence interval) were 0.095 (0.04 - 0.22), 1.14 (1.04 - 1.25), 1.04 (1.002 - 1.08) and 11.82 (5.47 - 69.40), respectively.* ***Conclusion:*** *Even in a setting with high fatality rates, high risk of mortality in neonatal sepsis can be identified and targeted for intensive intervention.*

Key words: *Neonatal sepsis, Mortality, Septic shock, Metabolic acidosis, Neutropenia.*

SEPSIS is a frequent and serious event which threatens survival during the neonatal period. The morbidity and mortality rate from neonatal sepsis continues to be high the world over inspite of the development of broad spectrum antibiotics and technological advances in life support therapy(l-7). The reasons that some neonates with sepsis die while others survive is still not clear. A reduction in sepsis related mortality may be possible by identifying high risk neonates and targeting them for intensive therapy. Earlier reports on mortality in neonatal sepsis have been simple correlation studies done in an uncontrolled way(8-12). There is a paucity of reports on risk factors in fatal neonatal sepsis using multivariate statistical analysis to establish risk factors for fatality with adjustment for potential confounders. It has also been recently realized that inability to identify patients at greatest risk is causing problems for researchers who design clinical trials for the innovative therapies to fight sepsis, systemic inflammatory response syndrome and multiple organ dysfunction syndrome(13). The present study was therefore designed to evaluate the risk factors for fatal neonatal sepsis using multivariate logistic regression analysis.

Subjects and Methods

This prospective study was done on neonates admitted to the Referral Neonatal Unit of Lok Nayak Hospital, New Delhi, which predominantly serves the poorer strata of the society. The neonates are mostly referred from hospitals with poor facilities for neonatal care and are brought late in critically sick condition.

Inclusion criteria consisted of all of the following: *(i)* Clincial feature of neonatal sepsis; *(ii)* Physical examination demonstrating either circulatory or respiratory dysfunction. Circulatory dysfunction was evidenced by the presence of tachycardia (heart rate more than 160/minute) or bradycardia (less than 100/minute) or capillary refill time more than 3 seconds. Respiratory dysfunction was evidenced by the presence of grunting, flaring retractions, tachypnea (more than 60 breaths/minute) or apnea lasting more than 15 seconds; and *(iii)* One or more of the following laboratory criteria: *(a)* Positive blood culture, *(b)* Polymorphonuclear band cells more than 20%, *(c)* Elevated C-reactive protein(14).

One hundred and seventy one neonates were enrolled for the study. Findings of clinical examination and investigations on the day of admission were recorded in a structured proforma. Prothrombin time was estimated 6 hours after administration of injection vitamin K in all neonates. The neonates were divided into various stages of systemic inflammatory response syndrome namely sepsis, sepsis syndrome, early septic shock, refractory septic shock and multiple organ dysfunction syndrome(15). Interpretation of neutrophil counts was done as suggested earlier(16).

Management of the septic neonates included administration of parenteral fluids, vasoactive agents and oxygen for hemodyanamic stability and oxygenation of vital tissues (whenever required) and the use of adequate antimicrobial agents and early drainage or removal o£ purulent foci to achieve bacterial eradication(15).

The neonates were followed up to determine the final outcome. Those who died served as cases while those discharged after recovery were taken as controls. To find out the risk factors associated with mortality in neonatal sepsis, all clinical and investigative variables were first evaluated by univariate analysis. Chi Square and Fischer's exact test were used to analyze the significance of the differences. The factors found to be significant on univariate analysis were subsequently subjected to a stepwise multiple logistic regression analysis to evaluate the independent predictors of mortality due to neonatal sepsis.

Results

Out of 171 septic neonates, 83 (48.5%) died (cases) and 88 were discharged after they improved (controls). The stages of systemic inflammatory response syndrome at admission was sepsis in 49, sepsis syndrome in 66, early septic shock in 19 and refractory septic shock in 37 neonates. None of the neonates had multiple organ dysfunction at admission.

The significant risk factors for mortality due to sepsis on univariate analysis were weight, gestational age, age of onset of sepsis, hypothermia, requirement of IPPV and presence of refractory septic shock *(Table I).* Significant investigative findings included neutropenia, metabolic acidosis and raised prothrombin time.

On multivariate analysis, the significant independent risk factors for mortality were neutropenia, increased negative base excess and prothrombin time and presence of refractory septic shock *(Table II).*

Age of onset of sepsis was an independent clinical predictor. However, this parameter did not remain statistically significant when laboratory variables were also included in the model. Refractory septic shock remained an independently significant predictor of mortality even in the presence of laboratory variables *(Table III).*

Discussion

Sepsis is a major cause of neonatal mortality. The present study highlights the identification of refractory septic shock,

TABLE I–*Descriptive Statistics of the Cases and Controls.*

Factors	Deaths (n=83)	Discharged (n=88)	p value
Weight (g) Mean (SD)	1803. 61 (682)	2311 (696)	< 0.00001
Gestational age (weeks) Mean (SD)	35 (4.0)	38 (2.7)	< 0.0001
Age of onset (days) Mean (SD)	3 (5.3)	9 (8.3)	< 0.00001
Male sex %	70	74	0.68
Home delivery (number)	39	48	0.40
Sclerema	10	3	0.06
Apnea	9	3	0.11
Hypothermia	47	20	< 0.00001
IPPV required	18	5	0.0044
Refractory septic shock	34	3	< 0.00001
Neutropenia	67	4	< 0.00001
PH mean (SD)	7.14 (0.15)	7.26 (0.12)	< 0.00001
Base deficit mean (SD)	15.83 (6.77)	9.61 (5.8)	< 0.00001
Positive blood culture	43	35	0.08
Prothrombin time (sec) Mean (SD)	28.1 (15.33)	23.9 (12.05)	0.0025

neutropenia, metabolic acidosis and increased prothrombin time as significant independent predictors of mortality in neonatal sepsis.

In the present study, neutropenia was the most significant risk factor for death from neonatal sepsis. In an earlier report(17), 16 out of 26 neonates with sepsis and neutropenia had severe depletion of the neutrophil storage pool. Mortality was high when neutrophil storage pool was depleted and granulocyte transfusion led to improved survival. In a randomized controlled trial(18) of exchange transfusion in neonatal sepsis with neutropenia, improvement in neutrophil count and function was documented after exchange transfusion.

Base deficit and refractory septic shock were the other independent risk factors for fatality in sepsis in our study. Refractory septic shock occurs due to vasodilatation, capillary leak and endothelial damage. Current evidence indicates that these pathophysiological effects appear to be mediated by proinflammatory cytokines activated in response to microbial components in the vascular compartment (19-21). High values for tumor necrosis factor, interleukin-1 and also

TABLE II–*Unweighted Multiple Logistic Regression (All Clinical and Laboratory Variables).*

Predictor Variables	Coefficient	Std Error	Adjusted Odds Ratio (95% CI)	T Ratio	P value
Gestational age	– 0.0755	0.1266	0.93 (0.72-1.19)	– 0.60	0.5591
Weight	– 0.0003	0.0006	0.99 (0.99-1.0008)	– 0.51	0.6167
Age of onset of sepsis	– 0.0060	0.0386	0.99 (0.92-1.07)	– 0.16	0.8494
Hypothermia	– 0.0415	0.6549	0.66 (0.18-2.23)	– 0.63	0.5340
IPPV	0.5769	0.9926	1.78 (0.23-12.94)	0.58	0.5692
Absolute neutrophil count	– 2.3552	0.4287	0.09 (0.04-0.22)	– 5.49	0.00001
Base deficit	– 0.1345	0.0475	1.14 (1.04-1.25)	2.83	0.0052
Prothrombin time	– 0.0415	0.0198	1.04 (1.002-1.09)	2.10	0.0351
Refractory septic shock	2.4678	0.8881	11.82 (5.47-69.40)	2.78	0.0061

interleukin-6 in plasma of children with sepsis have been correlated with increased fatality rates(14). Interleukin-1 beta plasma levels during sepsis in neonates appear to be correlated with the decrease in diastolic tension according to birth weight(21). However, it is not feasible to estimate the levels of these cytokines routinely.

Increased prothrombin time was another independent risk factor for fatality in our study. In the septic neonates who had received Vitamin K, increased prothrombin time probably reflected activation of the coagulation cascade. A complete coagulogram was not feasible. In this context, it is pertinent to note that the present study was intended to evaluate only those risk factors available routinely for septic neonates.

Multivariate analysis limited to clinical factors yielded refractory septic shock and age of onset of sepsis as independent predictors of death. However, age of onset of sepsis lost significance when laboratory variables were also included in the analysis. Early onset of sepsis has been associated with high mortality in earlier studies(8,22) while other reports did not observe this association(10-23). In a series(24), higher mortality was documented in early onset sepsis due to group B streptococcus but not in sepsis due to *E. coli.*

In conclusion, even with routinely available clinical and laboratory parameters, risk of fatality can be identified in neonatal sepsis. There is an urgent need for further studies to identify risk factors before the disease reaches a critical stage. Newer modalities of treat-

TABLE III–*Unweighted Multiple Logistic Regression (Clinical Variables).*

Predictor Variables	Coefficient	Std Error	Adjusted Odds Ratio (95% CI)	T Ratio	p value
Gestational age	– 0.0421	0.0867	0.96 (0.81-1.13)	– 0.48	0.6338
Weight	– 0.0006	0.0004	0.99 (0.99-1.0002)	– 1.44	0.1464
Age of onset of sepsis	– 0.1051	0.0319	0.90 (0.84-0.96)	– 3.29	0.0014
Hypothermia	0.0265	0.4508	1.03 (0.42-2.53)	0.06	0.9081
Refractory septic shock	3.6531	0.7146	14.15 (3.42-58.56)	3.71	0.0004
IPPV	0.5771	0.7293	1.78 (0.42-7.64)	0.79	0.4350

ment of neonatal sepsis need evaluation using high risk factors as indicators of severity.

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