ROLE OF MATERNAL RISK FACTORS AND NEONATAL CLINICAL FEATURES IN DIAGNOSIS OF NEONATAL SEPSIS: A CASE CONTROL STUDY

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ABSTRACT

BACKGROUND

Sepsis is responsible for 30-50% of the total neonatal deaths in developing countries and is considered the commonest cause of neonatal mortality. Neonatal sepsis has wide range of presentations with number of predisposing factors. Our study aims at detecting the risk factors of neonatal sepsis and to describe the clinical features and laboratory profile of neonates started on intravenous antibiotics for neonatal sepsis.

METHODS

120 neonates (60 cases and 60 controls) admitted in the department of child health were enrolled in the present case control study and all cases were subjected to diagnostic evaluation and data was collected using restructured case record forms which included perinatal history, signs and symptoms associated with sepsis and laboratory investigations. Institutional Ethics Committee approved the study and written informed consent was obtained from all consenting mothers. Parameters are expressed as mean (SD) and as proportions.

RESULTS

52.5% neonates and 55% cases were males. 25% of cases were preterm deliveries and 21.7% cases were small for gestational age. Premature rupture of membranes (PROM), maternal urinary tract infections (UTI), and gestational diabetes mellitus (GDM) were seen in 16.7%, 10% and 28.3% cases. Hypothermia was a symptom of sepsis in 28.3% while fever was a symptom in 21.7% cases. CRP elevation and toxic granulations were seen in 75% and 33.3% cases. 6.7% cases had a positive blood culture.

CONCLUSIONS

Manifestations of neonatal sepsis are non-specific. A high index of suspicion with or without laboratory evidences of sepsis is the key for early diagnosis. Prompt institution of antibiotic therapy and supportive care will save most of the cases of neonatal sepsis.

KEYWORDS

Neonatal Sepsis, CRP, Hypothermia, Toxic Granulations.

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BACKGROUND

Neonatal sepsis is a group of symptoms and signs of infection commonly occurring together with or without accompanying bacteraemia in the first month of life. It encompasses septicaemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Sepsis is responsible for 30-50% of the total neonatal deaths in developing countries and is considered the commonest cause of neonatal mortality.[1,2] Neonatal sepsis is one of the leading cause of mortality and morbidity among term, preterm and very low birth weight infants in neonatal intensive care units.[3-5] Sepsis usually presents as non-specific symptoms and signs such as cyanosis, apnoea, hypothermia, feeding difficulty, bulging fontanelle, unexplained jaundice and mostly 'just not looking right'.[6,7] 20% of neonates develop sepsis and 1% die of sepsis related causes[2] and the incidence of sepsis in asymptomatic neonates is not rare.[8] The prevalence of sepsis among neonates presenting with fever is 10%[9] this is applicable mostly to term neonates since most of the preterm new-

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borns show hypothermia as symptom of sepsis due to their impaired temperature regulation especially in the initial two days[10,11] and also the use of incubators in preterm neonates reduces the scientific validity of using body temperature as an assessment tool for diagnosing sepsis[12]. Respiratory distress can be the sole manifestation of sepsis with or without pneumonia is often misinterpreted as transient tachypnoea of new born. Sepsis deteriorates very rapidly, and the mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care. Also, the identification of metastatic foci of infection, disseminated intravascular coagulation, congestive cardiac failure and shock has to be identified and treated. Sepsis is usually classified as early onset (within 3 days of delivery) and is due to vertical transmission and late onset (after 3 days) and is due to horizontal transmission of pathogens. Some paediatricians classify sepsis as early (within 4 days), late (5-30 days) and late-late onset (>30 days). Very low birth weight infants are at high risk of late onset sepsis. Group B streptococcus, Escherichia coli and Listeria monocytogenes have been implicated in early onset sepsis[13] and coagulase negative staphylococci, Pseudomonas aeruginosa, Candida albicans, Serratia marcescens, and E. coli are pathogenic organisms commonly associated with late onset sepsis.[14] Hospital based studies suggest a 30 in 1000 live born and community-based studies suggest 2.1-17% of all live births in India. <50% of sepsis related neonatal deaths in our country occur in the first week of life, 30% in the second week and one-fifths in weeks 3-4.[15] Since sepsis is an inflammatory response, isolation the causative organism is considered gold standard for the diagnosis.[16] Since the culture is time intensive and the absence of microorganisms does not exclude sepsis, panel of investigations are recommended for sepsis. Low white cell count with absolute neutrophil count (ANC) and high immature to total neutrophil (I:T) ratio points towards sepsis. C-reactive protein (CRP) is an acute phase reactant synthesized by the liver and has been extensively studied for its utility in sepsis.

With improved obstetrical management and evidence-based use of intrapartum antimicrobial therapy, early-onset neonatal sepsis is becoming less frequent. However, early-onset sepsis remains one of the most common causes of neonatal morbidity and mortality in the preterm population. The identification of neonates at risk for early-onset sepsis is frequently based on a constellation of perinatal risk factors that are neither sensitive nor specific. Furthermore, diagnostic tests for neonatal sepsis have a poor positive predictive accuracy. Our study aims at detecting the risk factors of neonatal sepsis and to describe the clinical features and laboratory profile of neonates started in intravenous antibiotics for neonatal sepsis.

METHODS

Our case control study enrolled neonates admitted in department of child health, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum during a period of 1 year between 2014 and 2015**.** Cases were neonates diagnosed as having sepsis and who were started on intravenous antibiotics and controls were normal healthy neonates admitted in postnatal ward. Neonates with congenital defects and metabolic disorders were excluded from the study. Sample size was calculated as 120 (60 cases and 60 controls) assuming α of 0.05, β of 0.2 and 80% power. Case control design was used to describe the maternal risk factors for neonatal sepsis and descriptive methodology was used to describe the clinical features and laboratory profile of neonatal sepsis. All cases were subjected to diagnostic evaluation and data was collected using restructured case record forms. Data collected included perinatal history (premature rupture of membranes (PROM), history of urinary tract infections (UTI), prolonged labour, history of gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), type of delivery), signs and symptoms associated with sepsis and the laboratory investigations. Study commenced after obtaining approval from Institutional Ethics Committee and written informed consent was obtained from all consenting mothers. All parameters were analysed using free to use software R ®™ and parameters are expressed as mean (standard deviation (SD)) and as proportions.

RESULTS

Our case control study enrolled 120 neonates (60 cases and 60 controls) of which 52.5% (n=63) were males. Among the neonates with sepsis 55% (n=33) were males and 45% (n=25) were females and among controls 50% were males (n=30) and 50% (n=30) were females. 25% (n=15) neonates with sepsis were preterm deliveries and 75% (n=45) were term deliveries. Among controls 10% (n=6) were preterm and 90% (n=54) were term deliveries. 21.7% (n=13) neonates were small for gestational age (SGA) (table 1) and the maternal risk factors are demonstrated in table 2.

Gestational Age	Cases n (%)	Controls n (%)
SGA	13 (21.7%)	5 (8.3%)
Appropriate for gestational age (AGA)	45 (75%)	53 (88.3%)
Large for gestational age (LGA)	2 (3.3%)	2 (3.3%)

Table 1. Proportion of Neonates According to Size and Gestational Age

Maternal Risk Factor	Cases n (%)	Controls n (%)
PROM	10 (16.7%)	1 (1.7%)
Maternal UTI	6 (10%)	0
Prolonged Labour	1 (1.7%)	0
GDM	17 (28.3%)	13 (21.7%)
PIH	5 (8.3%)	8 (13.3%)

Table 2. Maternal Risk Factors Among Cases and Controls

Among cases 53.3% (n=32) were normal deliveries and 46.7% (n=28) were instrumental deliveries and among controls 51.7% (n=31) were normal deliveries and 48.3% (n=29) were instrumental deliveries. Only 21.7% (n=13) neonates with sepsis had fever and 6.7% (n=4) controls had fever. 28.3% (n=17) neonates with sepsis had hypothermia

and none of the controls had hypothermia. None of controls reported poor feeding and 63.3% (n=38) neonates with sepsis had poor feeding. 23.3% (n=14) cases and 13.3% (n=8) controls had vomiting. 46.7% (n=28) cases had respiratory distress while none of the controls had the same symptom. 60% (n=36) neonates had lethargy while none of the controls had the same symptom. Proportion of neonates with jaundice, convulsions and irritability are demonstrated in table 3 and the laboratory parameters of neonates are demonstrated in table 4.

Symptom	Cases	Controls
Jaundice	23 (38.3%)	17 (28.3%)
Convulsions	1 (1.7%)	0
Irritability	9 (15%)	1 (1.7%)

Table 3. Proportion of Participants with Jaundice Among Cases and Controls

Parameter	n (%)
CRP ≥0.6	45 (75%)
ANC <1800 cells/mm3	2 (3.3%)
Toxic granulations	20 (33.3)
I:T ratio ≥0.2	12 (20)
Total leukocyte count ≥ 5000 cells/mm3	15 (25)
Platelet count <1.5 lakh cells/mm3	3 (5)
Positive blood culture	4 (6.7)

Table 4. Laboratory Parameters Among Neonates with Sepsis

DISCUSSION

Neonatal sepsis is the single most important cause of neonatal deaths in the community, accounting for over half of them. If diagnosed early and treated aggressively with antibiotics and with good supportive care, it is possible to save most. 52.5% of the neonates were males which corresponds to the global average of 1050 males for every 1000 females[17] but does not correspond with the Kerala gender ratio of 1050 males for every 1041 females.[17] Geographical and institutional differences could contribute to this observation. 55% of neonates with sepsis were males, which is probably due to the gender specific genes involved in the immune system predisposing the male phenotype to higher risk of sepsis.[18,19] 25% of neonates with sepsis were preterm. Wide variability of the association of preterm delivery and neonatal sepsis have been reported with corresponding reports[20] and reports of a very high proportion (~77%) of neonates with sepsis being preterm. 75% of the neonates with sepsis were AGA, 21.7% were SGA and 3.3% were LGA. Sepsis has been associated with SGA[21] but our study did not demonstrate such an association. 6.7% neonates with sepsis had an APGAR score less than 6 and all controls had APGAR higher than 6. Preterm neonates and neonates with lower APGAR score are at higher risk of developing respiratory complications and may require mechanical ventilation and subsequent sepsis.

The most common maternal risk factor associated with neonatal sepsis was PROM (16.7% cases and 1.7% controls). PROM is a significant risk factor for early onset neonatal sepsis[22] with higher Odds of neonatal sepsis in neonates of mothers with PROM.[23] The longer the duration of ruptured membranes, the higher the risk of sepsis. Maternal UTI was present in 10% of cases and was absent among controls. UTI during term pregnancy is associated with higher risk of vertical transmission intrapartum and subsequent neonatal sepsis.[24] GDM was present in 28.3% cases and 21.7% controls and has not yet been described as a predictor of neonatal sepsis and no association of GDM with organisms producing sepsis has also been reported.[25] This could be due to higher risk of UTI,[26] PROM[27] and other infections among mothers with GDM predisposing to neonatal sepsis. Owing to the high prevalence of GDM among Keralites[28] this observation requires further evaluation. Instrumental delivery has been reported as a risk factor for neonatal sepsis however we did not find higher proportion of instrumental delivery among neonates with sepsis. Higher proportion of controls had PIH (13.3%), the association between PIH and neonatal sepsis require further evaluation as to whether PIH has protective effect or predispose to neonatal sepsis. Prolonged labour has also been reported as a risk factor for neonatal sepsis but was observed in only 1.7% cases and were absent among controls.

Hypothermia (28.3%) was a predominant symptom of sepsis in comparison to fever (21.7%). This has been described as due to non-development of temperature regulation in early neonatal life and is more commonly seen among preterm neonates. 63.3% neonates with sepsis had poor feeding and is reported as a symptom prevalent in initial four days of neonatal period more commonly during the 3rd and 4th day of neonatal life.[29] Vomiting was observed among 23% neonates and has been described as a feature of late onset neonatal sepsis.[29] Respiratory distress was a symptom of neonatal sepsis in 47% neonates while previous reports suggest ~28% respiratory distress among neonatal sepsis.[29] Lethargy was seen in 60% cases in contrast to reports of lethargy in 15% neonates with sepsis. Jaundice was reported in 38% though previous reports suggest it in 7.4% neonates with sepsis. Convulsions and irritability were seen in 1.7% and 15% cases. These differences in presentation could be due to the wide symptomatology of sepsis presentation. A field trial conducted in 39 villages in India has demonstrated that 2 of 7 clinical signs such as reduced or absent sucking, weak or no cry, limbs becoming limp, vomiting or abdominal distension, baby who is cold to touch, severe chest in drawing and presence of umbilical infection predicted sepsis with 100% sensitivity, 92% specificity, 27.2% positive predictive value and 100% negative predictive value.[30]

Elevated CRP was observed among 75% of the neonates with sepsis and has been reported to have 70% accuracy in detecting sepsis.[31] Inflammation triggers hepatocytes to produce C reactive protein and hence the elevated levels in neonates with sepsis. ANC <1800 cells/mm^3 were observed in 3.3% cases, toxic granulations were observed in 33.3% cases and abnormal I:T ratio were observed in 20% cases. Abnormal ANC and elevated I:T ratio are considered as strong indicators of neonatal sepsis. Leucocytosis was present in 25% cases; positive blood

culture was demonstrated in 6.7% cases and thrombocytopenia in 5% cases. Organisms isolated from culture were Enterobacter spp., Klebsiella spp. and E. coli. Published literature on the usefulness of I:T ratio suggest the sensitivity of 93% and suggests identification of over 90% of neonatal sepsis.[32] In the initial 3 days of life leukopenia, neutropenia, elevated I:T ratio, elevated I:M ratio are good diagnostic markers of neonatal sepsis.[33] 'STOPS' scoring showed 78.3% sepsis neonates had a score less than 3, 15% had score between 3 to 5 and 6.7% had score above 5. The STOPS score of >5 indicates intervention and mechanical ventilation.

CONCLUSIONS

Higher proportion of SGA neonates developed sepsis. Significant maternal risk factors were PROM, maternal UTI and GDM. PIH had inverse relationship with neonatal sepsis. Fever was not a predominant symptom of sepsis, but hypothermia was a significant symptom. Higher proportion of jaundice and irritability were seen in sepsis. Elevated CRP was an important laboratory finding in sepsis and toxic granulations were important finding too. Only few neonates had a positive blood culture for sepsis. Manifestations of neonatal sepsis are non-specific. A high index of suspicion with or without laboratory evidences of sepsis is the key for early diagnosis. Prompt institution of antibiotic therapy and supportive care will save most of the cases of neonatal sepsis.

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