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Original Article

The clinical spectrum and outcome of neonatal sepsis in a neonatal intensive care unit at a tertiary care hospital in western Nepal: January 2000 to December 2005 - A retrospective study.

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Abstract. Sepsis is the commonest cause of neonatal mortality. However the incidence of the latter varies with the geographical area, the socio-economic structure and various customs and practices in the perinatal period. Till date there have been no published data regarding the latter in Nepal. With the neonatal services coming of age in Nepal it becomes pertinent to study the magnitude and characteristics of the burden of neonatal sepsis**.** We conducted a retrospective study over a period of six years to elucidate the risk factors, clinical spectrum, diagnostic parameters and the outcome of neonatal sepsis at a tertiary care neonatal intensive care unit. In all 265 cases of suspected sepsis were screened using a panel consisting of C – reactive protein, absolute neutrophil count and immature to total neutrophil count ratio and subsequently confirmed by cultures. The cases were early onset (n=44), late onset (n=56) and nosocomial groups (n=40). The data for the intramural (n=32) and extramural (n=68) cases was analyzed separately. In all 265 neonates (male: female = 1.86:1) were screened for sepsis, out of which 183 resulted a positive screen, of which, 100 had pathogenic organisms (37.76%). Prematurity (22 to 71%) was most frequently associated with all the categories: suspect, early onset, late onset, nosocomial, irrespective of whether they were in- or out-born. The major risk factor associated with out-born babies was asepsis during labour (57.4%). Respiratory signs and symptoms were commoner in the in-borns as well as the nosocomials. The commonest complication associated with neonatal sepsis in our study was exaggeration of neonatal jaundice/hepatitis (80 to 92%). The sensitivity and specificity for C – reactive protein, immature to total neutrophil count and absolute neutrophil count were found to be 93% and 49.7%, 36% and 75.6% and 20% and 83.4% respectively. Among the culture positive neonates (n=100), 32 were in-house deliveries, and the rest were out-born. The frequency of early and late-onset sepsis was similar. In all there were 131 isolates from blood, cerebrospinal fluid and urine, out of which 38 (29.0%) were in the in-born babies. Nosocomial sepsis accounted for 44 (33.59 %) of the isolates out of both the in and out-born babies combined. The mortality (10%) and sequelae (7.5%) was higher in the nosocomial sepsis group. We observed that there is a high rate of aseptic home deliveries. Nosocomial sepsis was an important problem in the study though the outcome was not un-encouraging. There is a need for extension and intensification of the maternal and child health services in Nepal.

Key words: Extramural and nosocomial septicemia, intramural, neonatal sepsis

1. Introduction

The incidence of neonatal septicemia in the developing nations (39/1000 live births) is much higher than that reported from their fortunate counterparts (1 to 10/1000 live births) (1,2). Neonatal sepsis is one of the commonest causes of neonatal mortality in the developing world, hence is the commonest provisional diagnosis on admission at most referral facilities (3,4). However the incidence of the neonatal sepsis varies with the geographical area, the socio-economic structure and various customs and practices in the perinatal period as does the clinical presentation. With limited resources, delayed referral and often unethical pre-treatment

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with different drugs, the diagnosis of neonatal sepsis is often challenging in this part of the country and makes the treatment more difficult, prolonged and costly resulting in poor outcome: both immediate and the long term morbidity. The present study is a retrospective analysis of the scenario at a tertiary care referral hospital in the western region of Nepal and the first of its kind to be reported.

2. Materials and methods

We conducted a retrospective analysis of the cases admitted to the neonatal intensive care unit (NICU) of Manipal Teaching Hospital, Manipal College of Medical Sciences, Pokhara, Nepal and studied the clinical pattern of septicemia, its correlation with the septic screen and the incidence of culture positive sepsis during the period starting from 1st January 2000 to 31st December, 2005. The management of the cases was according to the written standard protocols in the unit. The neonates who presented with signs and symptoms of septicemia, with or without pneumonia and/or meningitis were studied in retrospect and a detailed record of the maturity, age at onset, sex, birth weight (weight on admission for home deliveries), symptoms and signs along with the maternal risk factors was made. The cases with suspect sepsis were screened using C-reactive protein (CRP, quantitative nephelometric test), the white blood cell (WBC), absolute neutrophil count (ANC), the immature to total neutrophil (I/T) ratio and the presence of toxic granules in the WBC's. The CRP was done after four hours of life in case of in-born babies with risk factors with or without symptoms and on admission for out-born babies. Blood culture was also done in all the cases while cerebrospinal fluid (CSF) was analyzed only in those neonates with suspected meningitis and the ones with late onset septicemia. Urine microscopy and cultures were done routinely for all neonates. Other investigations were done as required. The cases with suspect sepsis were started empirically on antibiotics, which were changed according to the sensitivity pattern once the culture report was available or stopped after two days if both the screen and cultures were negative, while in case of a positive screen with negative cultures the antibiotics were given for seven days. Meanwhile the clinical status of the neonate was closely observed. Deteriorating clinical picture or no response to antibiotic therapy over a reasonable period warranted repeat cultures. The results were categorized into intramural or in-born babies, extramural or out-born babies, early onset (culture positive within 7 postnatal days) late onset (culture positive after 7 postnatal days) and nosocomial sepsis (defined as an organism being isolated after the 72 hours of admission, wherein the initial screen and culture was negative). The following aspects were studied:

- The relative frequency of the risk factors in neonatal sepsis.
- The clinical spectrum of neonatal sepsis at the NICU.
- A comparison of the diagnostic methods.
- The clinical outcome in terms of mortality and morbidity (duration of antibiotics, hospital stay and sequela if any) was also studied.

3. Results

In all 265 neonates (male: female = 1.86:1) were screened for sepsis, out of which 183 (69.06 %) resulted a positive screen i.e. any two out of CRP (>6mg/dL), I/T ratio (>20%) and ANC less or more than the individual limits for the given postnatal age (5). Out of these 183 neonates with a positive sepsis screen, 117 neonates had positive cultures but on excluding the contaminants/skin commensals (B. subtilis, micrococcus spp. etc), 100 had pathogenic organisms (37.76% of the total population screened). They were further categorized into in-born (n=32), out-born (n=68), early onset (n=44), late onset (n=56) and nosocomial groups (n=40).

There were various risk factors identified with the suspected cases (Table 1). Prematurity (22% to 71% of the cases) was most frequently associated with all the categories: suspect, early onset, late onset, nosocomial, irrespective of whether they were in- or out-born. Invasive resuscitation at birth (71%), instrumentation/invasive procedures during delivery (68%), leaking per vaginum > 24 hours (31%) and unclean methods of per-vaginal examination (home deliveries) (23%) were additionally commonly associated with early onset sepsis. Cases with late onset and nosocomial sepsis were commonly associated with a prolonged hospital stay (52% and 82% respectively). Intubation at birth was most frequently associated with in-born neonates (84%). The major risk factor associated with out-born babies was unclean methods during labour (57.4%). All the cases with major surgical intervention (n=4) and ventilation (n=3) developed nosocomial sepsis.

The most common clinical features of sepsis overall were lethargy, poor feeding, temperature

instability and respiratory distress (Table 2). Respiratory signs and symptoms were commoner in the intramural as well as the nosocomial group (90-100%), along with gastrointestinal problems like abdominal distension, feed intolerance, gastric aspirates and features of neonatal enterocolitis (NNEC) (62-75%). Diarrhea (59%) and sclerema (21%) were commoner in the out-born babies than in the others. The commonest complication associated with neonatal sepsis in our study was exaggeration of neonatal jaundice/hepatitis (80 to 92%). Shock, irrespective of the cause was more commonly seen in the out-borns and nosocomials: 41% and 50% respectively. The frequency of seizures was as much so in the early onset sepsis as in the nosocomials (30%). Two cases developed renal failure.

The sensitivity and specificity for CRP was 93% and 49.7%, I/T ratio was 36% and 75.6% and ANC was 20% and 83.4% respectively. The total number of positive cultures was 131 from 100 subjects from blood, CSF and urine. Early onset sepsis accounted for 49.62 % [n=66] of the isolates with the mean age at presentation of 3.96 days (95% CI = ± 0.97) (Table 3). The frequency of late onset sepsis was also similar with a mean age at onset being 13 days (95% CI = ±1.96) [range = 8 to 25 days]. There was no significant difference in the parameters used for septic screening in either of the groups (Table 3). The mean (± SD) day of admission on isolation of a pathogenic organism was 5.1 (±2.4) days (range 4 to 12 days) in the nosocomial group, 2.3 ± 1.7 in early onset sepsis and 2.4 ± 3.1 in late onset sepsis cases. Among the culture positive neonates (n=100), 32 were intramural deliveries, and the rest were extramural. In all there were 131 isolates from blood, CSF and urine, out of which 38 (29.0%) were in the intramural babies. Nosocomial sepsis accounted for 44 (33.59 %) of the intramural and extramural cases combined. There was an evidence of meningitis (hypoglycorrhachia and/or pleocytosis) in 26% of the out-born babies with a positive blood culture, which was higher than that in the other two categories. CSF culture was positive in 3.13%, 4.41%, and 5.0% of intramural, extramural and nosocomial cases respectively. There was only one case where an organism was from the CSF

Table 1. The risk factors observed in the various categories of neonatal sepsis*

Risk factors for neonatal sepsis	Screened population [n=265] (%)	Early onset sepsis [n=44] (%)	Late onset sepsis [n=56] (%)	In-born [n=32] (%)	Out-born [n=68] (%)	Nosocomial sepsis [n=40] (%)
Maternal fever within 1 wk.	14 (5.3)	7 (15.9)	4 (7.1)	4 (12.5)	4 (5.9)	2 (5.0)
Leaking per vaginum > 24 hrs.	33 (12.5)	**14 (31.8)**	8 (14.2)	**15 (46.8)**	4 (5.9)	4 (10.0)
Foul smelling liquor	8 (3.0)	5 (11.4)	2 (3.5)	4 (12.5)	1 (1.5)	2 (5.0)
Aseptic methods of p/v examination (home deliveries)	35 (13.2)	**10 (22.7)**	**20 (35.7)**	0	**39 (57.4)**	**22 (55.0)**
Instrumentation/invasive procedures during delivery	112 (42.3)	**30 (68.2)**	4 (7.1)	23 (71.9)	29 (42.6)	4 (10.0)
Prematurity	**188 (70.9)**	**10 (22.7)**	**34 (60.7)**	**17 (53.1)**	**27 (39.7)**	**20 (50.0)**
Invasive resuscitation at birth	155 (58.5)	**31 (70.5)**	12 (21.4)	**27 (84.3)**	12 (17.6)	12 (30.0)
Central venous cannulation/exchange transfusion	22 (8.3)	4 (9.1)	5 (8.9)	3 (9.3)	8 (11.8)	**7 (17.5)**
Hospital stay > 10 days	204 (77.0)	0	**29 (51.8)**	20 (62.5)	35 (51.5)	**33 (82.5)**
Neonatal ventilation	2 (0.6)	0	2 (3.6)	0	2 (2.9)	**3 (7.5)**
Congenital malformations	7 (2.6)	1 (2.3)	4 (7.1)	2 (6.3)	2 (2.9)	3 (7.5)
Major surgery	4 (1.2)	0	**4 (7.1)**	1 (3.1)	3 (4.4)	**4 (10.0)**

*The major factors have been highlighted in bold.

while the blood culture was sterile. There were neonates with polymicrobial sepsis simultaneously or sequentially (31 out of 131 isolates, 23.66%). Table – 3 provides the data for the mortality and morbidity amongst the cases studied in retrospect. The mortality (10%), sequela (7.5%) and duration of hospital stay (21.1 ± 8.21 days) were highest in the nosocomial sepsis group.

Table 2. A Comparison of the clinical features of sepsis in the different categories*

Clinical features of neonatal sepsis	Screened population [n=265] (%)	Early-onset sepsis [n=44] (%)	Late onset sepsis [n=56] (%)	In-born [n=32] (%)	Out-born [n=68](%)	Nosocomial sepsis [n=40] (%)
Lethargy	**202 (76.2)**	**38 (86.4)**	**55 (98.2)**	**25 (78.1)**	**68 (100)**	**40 (100)**
Poor feeding	**211 (79.6)**	**37 (84.1)**	**56 (100)**	**25 (78.1)**	**66 (97.1)**	**40 (100)**
Icterus	**227 (85.7)**	**40 90.9**	**45 (80.4)**	**29 (90.6)**	**55 (80.9)**	**37 (92.5)**
Temperature instability	178 (61.2)	24 (54.5)	51 (91.1)	30 (93.8)	52 (76.5)	35 (87.5)
Abdominal distension	**195 (73.6)**	18 (40.9)	21 (37.5)	**20 (62.5)**	23 (41.1)	**30 (75.0)**
Tachypnea chest retractions	**207 (78.1)**	**41 (93.1)**	**49 (87.5)**	**29 (90.6)**	**44 (64.7)**	**40 (100)**
Grunting	201 (75.8)	36 (81.8)	48 (85.7)	**29 (90.6)**	43 (63.2)	**40 (100)**
Diarrhea	165 (62.3)	30 (68.1)	4 (7.1)	19 (59.4)	**40 (58.8)**	7 (17.5)
Shock	98 (37.0)	12 (27.2)	21 (37.5)	10 (31.3)	**23 (41.1)**	**20 (50.0)**
Renal failure	4 (1.5)	1 (2.2)	2 (3.5)	0	0	**2 (5.0)**
Sclerema	9 (3.4)	2 (4.5)	2 (3.5)	0	**14 (20.6)**	10 (25.0)
Seizures	78 (29.4)	**13 (29.5)**	11 (19.6)	7 (21.8)	14 (20.6)	**12 (30.0)**
Bulging fontanels	10 (3.7)	3 (6.8)	7 (12.5)	7 (21.8)	6 (8.8)	**8 (20.0)**

*The major features have been highlighted in bold.

4. Discussion

Sepsis is one of the important causes of neonatal morbidity and mortality. The maternal genital flora is classically incriminated in early onset septicemia (first week) while late onset septicemia (onset > 7 days) is a usually result of invasive strains of organisms colonizing after birth and hence is a direct reflection of community acquired sepsis or hospital flora as the case may be (2). Immaturity of the immune system of the neonate and the various environmental factors complete the epidemiological triad trapping the compromised neonate in a vicious circle of cause and effect. Maternal fever with or without chorioamnionitis and the duration of hospital stay with or without invasive procedures have been identified as the commonest risk factors in early onset and nosocomial sepsis, respectively (6). In this retrospective analysis, though prolonged rupture of membranes (> 24 hours) was frequent in early onset sepsis, unclean method during delivery was commonly seen with out-born babies, highlighting the poor primary health care status in this part of the country. In case of the intramural sepsis, the data for the high vaginal swab and amniotic membrane cultures was inconsistent due to lack of reports and hence was not taken into account. This may be a lacuna in the study. Nosocomial sepsis results from invasion of the hospital flora colonizing the skin and indwelling catheters of the neonate. This is reflected in our analysis as prolonged hospital stay, exchange transfusions, invasive ventilation and major surgery were most frequently associated with nosocomial sepsis cases. Recycling of catheters/ tubes, maintaining stock solutions and the use of multi-dose vials of antibiotics are other potential sources which commonly escape notice! (7).

Neonatal sepsis often presents as a multi-organ dysfunction syndrome. It is a result of a systemic inflammatory response (SIRS) to the microbial insult. The neonate is trapped in a vicious cycle of interplay between endotoxemia and the inflammatory mediators (8-10). The current interest in the management of neonatal sepsis is on the antagonism of the mediators of inflammation using intravenous immunoglobulins (IVIG), (11-15) apart from antibiotics and exchange transfusion (16). Our experience with the use of IVIG has been so far rewarding in all the cases of proven sepsis in which they were

used. Respiratory signs and symptoms were predominant in our subjects. Endotoxic shock, disseminated intravascular coagulation and neonatal enterocolitis had worse prognosis in our cases (10). Meningitis is seen in up-to 30% of late-onset sepsis and carries a poor prognosis for the neurological outcome irrespective of the maturity (17).

Various screening tests are employed to identify neonatal sepsis with variable sensitivity and specificity (18-21). The septic screen employed in most cases was according to the unit protocol, videlicet CRP, ANC and I/T ratio. Presence of toxic granules in the neutrophils was also given cognisance in case the above tests were negative and the clinical state was suggestive of sepsis. The sensitivity and specificity of CRP was found to be 93% and 49.7 % respectively. The I/T ratio (>20% band cells) was also helpful in screening of sepsis. Of the three tests, the CRP was most sensitive while ANC was most specific. CRP is the most sensitive and widely used, however it is necessary to consider a sepsis panel of at least three tests out of which at least two should be positive for one to suspect septicemia with reasonable amount of certainty. One such reasonable panel would contain CRP, ANC, I/T ratio and/ or micro ESR (22). The CRP titers are useful in monitoring the disease progression (23), however recent evidence points out that one need not continue antibiotics till the latter is negative (24). The ANC is a direct indicator of the neutrophil storage pool in the affected neonate and lower values are logically more ominous (5). Recent research in this field has led to the usage of granulocyte and granulocyte-monocyte colony stimulating factors (G CSF, GM CSF) (5,25). However there is no compelling evidence for the justification of such therapy in the literature (26,27). Their cost and timely availability remains a major deterrent in further research being carried out in this part of the world. The presence of bandemia (>20%) indicates a shift to left in the neutrophil storage/circulatory pool, implying the host response to microbial stimulus (28). In our study the specificity of a high I/T ratio was much higher than the CRP which was more sensitive though. Blood culture is the gold standard for the confirmation of sepsis. Most of the out-born babies had received prior antibiotics which made the isolation rates lower than expected.

Table 3. A comparison of the diagnostic tests and the outcome of neonatal sepsis

Parameters	In-born (n= 32)	Out-born (n = 68)	Nosocomial (n= 40)
Age on admission (days)	2.13 ±1.75	9.38 ± 5.51	5.43 ± 3.21
Birth weight / weight on admission (grams)	2471.9 ± 653.3	2709.7 ± 821.5	2672 ± 788.4
Maturity (weeks)	37.3 ± 2.8	38.3 ± 3.2	38.8 ± 3.4
Hemoglobin on admission /screen (gr/dL)	15.2 ± 3.0	16.3 ± 2.74	16.9 ± 2.6
Total leukocyte count on admission / screen (x 10^3)/cc	12.719 ± 7.441	10.647 ± 6.174	12.223 ± 7.708
Absolute neutrophil count on admission/ screen (x 10^3)/cc	7.322±0.443	5.612±0.231	5.622±0.312
Immature to total neutrophil ratio on admission / screen (%)	13.4 ± 8.4	15 ± 7.37	14.2 ± 7.4
C-reactive protein on admission / screen (mg/dL)	16.3	15	15.7
Mean day of life on isolation	3.2 ±1.9	10.2 ± 5.6	11.71 ± 5.9
Mean day of admission on isolation	2.3 ± 1.7	2.4 ± 3.1	5.1 ± 2.4
Hospital stay (days)	16.1± 7.24	15.4 ± 7.76	21.1 ± 8.21
Isolation rates			
Blood, n (%)	32 (100%)	66 (97.06%)	36 (90.0%)
Cerebrospinal fluid (% of blood c/s + ve)	9.38 % (n=3)	25.76 % (n=17)	16.67 % (n=6)
Urine, n (%)	1 (3.13%)	6 (8.82%)	4 (10.0%)
Outcome			
Cured	28 (90.63%)	63 (92.65%)	33 (82.50%)
Death	1 (3.13%)	3 (4.41%)	4 (10.0%)
Sequelae	3 (6.24%)	2 (2.94%)	3 (7.50%)

5. Conclusion

Neonatal sepsis carries a high morbidity and mortality, more so in the developing nations (3,29-31). It is in fact the leading cause of neonatal mortality in these nations. Poor maternal health both pre- and post-conceptional and poor nutrition are common predisposing factors in neonatal sepsis. The picture is complicated by the high incidence of unsafe delivery practices, by the so called birth attendants in home deliveries (as depicted by the highest risk association of the latter with the out-born cases in our study). Nepal still has a poor rate of institutional deliveries and though the government has started providing incentives for the latter, the geographical barriers are a deterrent in achieving the ideal; not to mention the on-going political turmoil which has given a further setback to it. Nevertheless, considering the fact that this being a tertiary care, referral hospital, the mortality and morbidity due to sepsis has been kept away, which was probably due to a strict adherence to a written asepsis policy within the NICU and regular anti-biotic susceptibility surveillance within the hospital. However it is imperative that the neonatal culture and sensitivity and susceptibility patterns should be studied and reviewed from time to time to keep abreast with the problem of emerging antibiotics resistance with the heavy use of antibiotics in the NICU.

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