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Role of Haematological Factors in Early Diagnosis of Neonatal Sepsis – A Prospective Study.

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ABSTRACT

Background: Early onset sepsis is significantly associated with predisposing perinatal risk factors. Various hematological parameters like white blood cell count, absolute neutrophil count, immature to total neutrophil ratio, degenerative changes in neutrophils, platelet count, C - reactive protein and Erythrocyte Sedimentation Rate are good diagnostic tools, which are easily available as rapid screening tests with good sensitivity and negative predictive value. The aim of present study is to evaluate the efficiency of the various blood parameters either alone or in combination in the early diagnosis of the neonatal septicaemia. **Methods:** The prospective, cross sectional hospital based study conducted over a period of 2 years on 250 newborns. This study was done to find out the predisposing risk factors, utility of sepsis screen to diagnose sepsis that is to evaluate the efficacy of various hematological parameters in diagnosing early onset sepsis. **Results:** Absolute neutrophil count has 87.5% sensitivity, 83.65% specificity, 51.03% PPV and 79.5% NPV. Platelet count has 93.33% sensitivity, 25% specificity, 25.92% PPV and 93.02% NPV. C - reactive protein has 91.45% sensitivity, 85% specificity, 22.05% PPV and 86% NPV. Micro Erythrocyte Sedimentation Rate has 64.44% sensitivity, 51.25% specificity, 20.41% PPV and 76.64% NPV. **Conclusion:** Various hematological parameters like white blood cell count, absolute neutrophil count, immature to total neutrophil ratio, degenerative changes in neutrophils, platelet count, C-Reactive Protein and Erythrocyte Sedimentation Rate are good diagnostic tools, which are easily available as rapid screening tests with good sensitivity and negative predictive value.

Keywords: Haematological factors, early diagnosis, neonatal sepsis.

INTRODUCTION

Sepsis is the commonest cause of neonatal mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries.[1,2] Estimates show upto 20% of neonates develop sepsis while 1% die of sepsis related causes.[2] Sepsis related mortality is largely preventable if diagnosed early and treated aggressively with antibiotics and good supportive care.

Neonatal sepsis can be classified into two sub-types depending upon whether the onset of symptoms is before 72 hours of life (early onset) or later (late onset). Early-onset infections are caused by organisms prevalent in the maternal genital tract or in the delivery area. The associated factors for early-onset sepsis include low birth weight, prematurity, prolonged rupture of membranes; foul smelling liquor, multiple per vaginal examinations, maternal fever, difficult or prolonged labour and aspiration of meconium. Early onset sepsis manifests frequently as pneumonia and less commonly as septicaemia or meningitis.[3-5]

Late-onset septicaemia is caused by the organisms thriving in the external environment of the home or the hospital. The infection is often transmitted through the hands of the care-providers. The onset of symptoms is usually delayed beyond 72 hours after birth and the presentation is that of septicaemia, pneumonia or meningitis. The associated factors of late-onset sepsis include: low birth weight, lack of breastfeeding, superficial infections (pyoderma, umbilical sepsis), aspiration of feeds, disruption of skin integrity with needle pricks and use of intravenous fluids.[5,6]

Degenerative changes like degranulation, swelling, Pyknosis, toxic granulations, cytoplasmic vacuolization, Dohle bodies and ingested microorganisms are frequently seen within the neutrophils in the blood of patients with infection.[7,8] Toxic granules are primary granule (azurophilic granules) present within the cytoplasm of neutrophils; they are deeply eosinophilic, peroxide

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granules and stain more deeply than the granules within normal cells.[9]

Neonatal thrombocytopenia is defined as platelet count of less than 1,50,000/cumm in the newborn period.[10] Many studies reported that 50% of the newborns with neonatal sepsis had a platelet count below 1,00,000/cumm.[4,8,9] Contrary to this view, some researchers stated that thrombocytopenia occurring in sepsis was probably a result of increased destruction of platelets due to immune mechanisms.[5,6]

An elevated ESR is part and partial of the acute phase response. The development, almost fifty years ago of an erythrocyte sedimentation rate (ESR) by the use of a microhaematocrit tube and a few drops of capillary blood permitted the application of this test to very small infants. Attempts at standardization have shown that micro ESR increases slowly during the first weeks of life, perhaps as a result of rising fibrinogen and falling haematocrit levels.[10]

Researchers evaluated the usefulness of a serial study of C-reactive protein in the early detection of ne natal septicemia using commercially available latex agglutination slide test. Studies claimed that although the slide test may reliably indicate infection at an early stage in neonates, the C-reactive protein response is non-specific, as seen in a non-infected infant who showed signs of birth asphyxia with meconium aspiration.[11]

The inability of any single laboratory test to provide rapid, reliable and early identification of neonates with bacterial sepsis has led to efforts to devise a panel of screening tests combining data from several different determinants, as a means of increasing predictive accuracy. In general, the results have shown little increase in positive predictive accuracy compared with most of the individual tests.

The aim of present study is to evaluate the efficiency of the various blood parameters either alone or in combination in the early diagnosis of the neonatal septicaemia

MATERIALS AND METHODS

This is a prospective cross sectional hospital based study conducted in Pathology department and neonatology division of department of Pediatrics , in Rural Medical College Loni over a period of 2 years from august 2009 to july 2011. This study was done to find out the predisposing risk factors, utility of sepsis screen to diagnose sepsis , that is to evaluate the efficacy of various hematological parameters in diagnosing early onset sepsis and identification of causative organisms and its correlation with hematological parameters. The study was done on 250 neonates selected by stratified random sampling, out of which 45 had proven sepsis, 160 had probable sepsis based on clinical features and sepsis screen and 45 had no sepsis.

Exclusion criteria

1. Extreme prematurity (<28wks gestation).
2. Very low birth weight (< l000gms).
3. Multiple gestations.
4. Neonates with congenital anomalies.
5. Late onset sepsis (> 72 hrs of age).
6. Babies delivered outside the hospital and admitted.

Methods

1. A printed questionnaire will be used to elicit detailed maternal history.
2. A printed proforma for recording detailed history and thorough clinical examination for neonatal septicemia.
3. On the day of admission following samples will be collected for investigation and evaluation.
4. Using all aspectic precautions blood will be collected from peripheral vein prior to starting antibiotic treatment. 2.0 cc to be collected in EDTA (Ethylene diamine tetra acetic acid) bulb for examination of haemoglobin, total leukocyte count and platelet count, 2 cc blood will be collected in a plain bulb for C-Reactive protein estimation.
5. Heel prick method was used to obtain blood for estimation of micro Erythrocyte Sedimentation Rate using pre-heparinised tubes39 and for preparation of smears (two) for estimation of the differential leukocyte count, band cell count and immature : total neutrophil (I:T) ratio.

   Peripheral blood smear is prepared and stained with Leishman stain ,for which first air dry the film & flood the slide with the stain ,after 2 min., add double the volume of water and stain the film for 5-7 min., then wash it in a running buffered water ,air dry and observed under microscope.[8]

   “Toxic granulation” is the term used to describe density and number of granules that occurs regularly with bacterial infection and often with other causes of inflammation.[11]

   In blood film spread without delay the presence of vacuoles and toxic granules in neutrophils is indicative of severe sepsis.[12]

   Micro-erythrocyte sedimentation rate: Micro-ESR is a simple inexpensive though not very reliable test of neonatal infection. Normal value is up to 6mm in the first hour during the first 3 days of life. By the end of first month, maximum fall may be up to 11mm. During the neonatal period a value of more than 15mm is considered as suggestive of infection. Micro-ESR is obtained by collecting capillary blood in a standard preheparinized micro hematocrit tube (75mm length, internal diameter of 1.1 mm) and by reading the fall of erythrocyte column after 1 hour.[13]

   C-reactive protein: CRP is a non-specific marker of inflammation or tissue necrosis. Elevations in CRP are found in bacterial sepsis and meningitis. A single determination of CRP at birth lacks both sensitivity and specificity for infection, but serial CRP determination at birth, at 12 hours and beyond have been used to manage infants at risk for sepsis. We do

not use CRP measurements in the evaluation of infants at risk for sepsis.[14]

In present study CRP estimation is carried out at the time of admission to NICU (Neonatal Intensive Care Unit) and is done by kit method.

RESULTS

Table 1: Distribution of study sample among total live inborns in study period.

Total No. of Live Births N = 6482		Total No. of Study Sample N = 250	
Male	**Female**	**Male**	**Female**
3400(52.45%)	3082(47.55%)	149 (59.60%)	101 (40.40%)

Out of total live births of 6482, 3400(52.45%) were male and 3082(47.55%) females. In Study sample N=250, 149(59.60%) were male and 101(40.40%) females [Table 1].

Table 2: Sex wise distribution of cases of sepsis

No. Of Babies with Sepsis n = 205			
Male	**Percentage**	**Female**	**Percentage**
123	60%	82	40%

Value of Chi Square test = 1.33, d. f. = 1, Not significant, p>0.05

After applying Chi-square test there is no significant association between babies with sepsis and sex (i.e. p>0.05)

Among the babies with sepsis, 123(60%) were male and 82(40%) females. There was no significant difference in incidence of sepsis in male and female [Table 2].

Table 3(a): Birth weight distribution of study sample among total live inborns

Birth Weight (Gms)	Hospital Live Born Cases In 2 Years N= 6482			No. Of Study Samples N=250		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
≤ 1000	13	31	44	0	0	0
1001-1500	113	114	227	28	16	44
1501-2000	271	296	567	32	27	59
2001-2500	944	958	1902	41	25	66
2501-3000	1353	1265	2618	35	21	56
3001-3500	632	383	1015	12	11	23
>3500	74	35	109	1	1	2
Total	3400 (52.45%)	3082 (47.55%)	6482	149 (59.60%)	101 (40.40 %)	250

The study sample of babies in each weight category is representative of the population from which it is drawn. Among the 250 babies selected for the study, 149 (59.60%) babies were male and 101(40.40%) babies were female. Out of these 44 babies were born in BW(1001-1500gms), of which 28 were male and 16 were female; 59 babies were born in BW(1501-2000gms), among whom 32 were male and 27 were female; 66 babies were born in BW(2001-2500gms), among whom 41 were male and 25 were female; 56 babies were born in BW(2501-3000gms), among whom 35 were male and 21 were female; 23 babies were born in BW(3001-3500gms), among whom 12 were male and 11 were female; 2 babies were born with BW>3500gms, among whom 1 was male and 1 was female. Maximum number of study sample, were in group of 2001-2500gms [Table 3a].

Table 3(b): Comparison of Mean birth weight (gms).

	Male Mean ± SD	**Female Mean ± SD**	**Z value**	**'p' value**	**Significance**
Hospital live born cases (n=6482)	2589.18 ± 845.25 (n=3400)	2496.93 ± 862.74 (n=3082)	4.34	p<0.05	Significant
No. of study samples (n=250)	2163.83 ± 874.12 (n=149)	2123.08 ± 865.56 (n=101)	2.15	p<0.05	Significant

By applying Z test of difference between two means there is a significant difference between mean birth weight of male and female in hospital born cases and study sample cases (i.e. p<0.05) [Table 3b].

Table 4: Distribution of study sample (N = 250) for categorization of Sepsis.

Study Sample	Male	Female	Total
Proven sepsis	27	18	45(18.00%)
Probable sepsis	96	64	160(64.00%)
No sepsis	26	19	45(18.00%)
Total	149	101	250

Value of Chi Square test = 0.026, d. f. = 2, Not significant, p>0.05

After applying Chi-square test there is no significant association between sepsis cases and sex for categorization of Sepsis (i.e. p>0.05)

Among the 250 study sample group, 205 babies were categorized as Sepsis cases and 45(18.00%) babies were having no sepsis. 45(18.00%) cases were culture proven of which 27 were male and 18 were female. 160(64.00%) were probable sepsis of which 96 were male and 64 were female. In relation to total hospital deliveries incidence of Sepsis cases in males is 4.41% and in females is 3.28% [Table 4].

Table 5: Birth weight wise distribution of cases of sepsis (n=205).

Birth Weight (Gms)	No. Of Babies n = 205		
	Male	**Female**	**Total**
1001-1500	27	15	42(20.49%)
1501-2000	30	22	52(25.37%)
2001-2500	37	18	55(26.83%)
2501-3000	22	18	40(19.52%)
3001-3500	6	8	14(6.83%)
> 3500	1	1	2 (0.96%)
Total	123 (60%)	82 (40%)	205

Mean birth weight for total patients = 2135.87
Male: 2052.25 & Female: 1865.26
Value of Chi Square test = 19.82, d. f. = 5, significant, p<0.05

After applying Chi-square test there is a significant association between birth weight and cases of sepsis (i.e. p<0.05).

Among the 205 babies, 42(20.49%) babies were born in BW(1001-1500gms), of which 27 were male and 15 were female; 52(25.37%) babies were born in BW(1501-2000gms), among whom 30 were male and 22 were female; 55(26.83%) babies were born in BW(2001-2500gms), among whom 37 were male and 18 were female; 40(19.52%) babies were born in BW(2501-3000gms), among whom 22 were male and 18 were female; 14(6.83%) babies were born in BW(3001-3500gms), among whom 6 were male and 8 were female; 2(0.96%) babies were born with BW>3500gms, among whom 1 was male and 1 was female. Mean birth weight among male was 2052.25gms and female 1865.26gms. There is statistically significant association between low birth weight and sepsis [Table 5].

Table 6(a): Distribution of cases of sepsis (n=205) according to laboratory parameters of sepsis screen

Laboratory Parameters	Culture Positive N = 45	Culture Negative N =160	Total Cases N = 205	P- Value	Chi-squar value
Absolute neutrophil count <1750/cmm	9	20	29	P>0.05	1.62
Total white blood count <5000/cmm or >15,000/cmm	35	130	165	P>0.05	0.26
Immature/total neutrophil ratio ≥0.20	42	112	154	p<0.01*	10.232
Immature/total neutrophil ratio ≥0.40	15	10	25	p<0.001*	24.05
Toxic granules & cytoplasmic vacuoles in neutrophil	40	15	55	P<0.001*	113.11
Platelet count	42	120	162	P<0.01	7.12
CRP positive	43	152	195	p>0.05	0.02
Micro ESR > 15 mm/1st hour	20	78	98	p>0.05	0.26

* Highly significant

Table 6(b): Shows the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of sepsis screen parameters:

Laboratory Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Absolute neutrophil count <1750/cmm	87.5	83.65	51.03	79.55
Total white blood count <5000/mm3 or >15,000/mm3	77.78	58.75	21.21	75
Immature/total neutrophil ratio ≥0.20	93.33	30	67.27	94.12
Immature/total neutrophil ratio ≥0.40	98.25	93.75	60	83.33
Toxic granules & cytoplasmic vacuoles in neutrophil	88	90.62	72	96
Platelet count	93.33	25	25.92	93.02
CRP positive	91.45	85	22.05	86
Micro ESR > 15 mm/1st hour	64.44	51.25	20.41	76.64

Absolute neutrophil count has 87.5% sensitivity, 83.65% specificity, 51.03% PPV and 79.5% NPV. Total white blood count has sensitivity of 77.5% sensitivity, 58.75% specificity, 21.21% PPV and 75% NPV. Immature/Total neutrophil ratio >0.20 has a 93.33% sensitivity, 30% specificity, 67.27% PPV and 94.12% NPV. Immature/Total neutrophil ratio>0.4 has 98.25% sensitivity, 93.75% specificity, 60% PPV and 83.33% NPV. Toxic granules and cytoplasmic vacuoles in neutrophils has 88% sensitivity, 90.62% specificity, 72% PPV, 96% NPV. Platelet count has sensitivity 93.33%, specificity 25%, PPV 25.92%, NPV 93.02%. C-Reactive protein has 91.45% sensitivity, 85% specificity, 22.053% PPV and 86% NPV. Micro ESR has 64.44% sensitivity, 51.25% specificity, 20.41% PPV and 76.64% NPV [Table 6a,b].

DISCUSSION

Sepsis is the commonest cause of neonatal morbidity and mortality in India. This is a prospective cross sectional hospital based study done to find out risk factors and utility of sepsis screen to diagnose sepsis along with identification of causative organisms. The study was done on 250 neonates selected by stratified random sampling, out of which 45 had proven sepsis, 160 had probable sepsis based on clinical features and sepsis screen and 45 had no sepsis.

In present study number of babies included are 250 out of which 59.60% of babies were males and 40.40% were females, which is comparable with other studies showing a higher incidence in males. According to Kuruvilla et al (14) (n=250) incidence of early onset sepsis was 70% in males. Tallur et al (15) (n=203) had incidence of 63.63% in males. In present study 42(20.49%) babies were born in Birth

weight(1001-1500gms), of which 27 were male and 15 were female; 52(25.37%) babies were born in Birth weight(1501-2000gms), among whom 30 were male and 22 were female; 55(26.83%) babies were born in Birth weight(2001-2500gms), among whom 37 were male and 18 were female; 40(19.52%) babies were born in Birth weight(2501-3000gms), among whom 22 were male and 18 were female; 14(6.83%) babies were born in Birth weight(3001-3500gms), among whom 6 were male and 8 were female; 2(0.96%) babies were born with Birth weight>3500gms, among whom 1 was male and 1 was female. Mean birth weight for all patients was 2135.87gms, among male was 2052.25gms and female 1865.26gms. There is statistically significant association between low birth weight and sepsis, which is comparable with other studies showing a higher incidence among low birth weight.

In a Study conducted by Khatua et al,[15] (n=92) shown weight of 1-1.5kg in 6.52%, 1.5-2kg in 48.91%, 2-2.5kg in 23.91% and >2.5kg in 20.65% . Mean birth weight in study conducted by Kuruvilla et al (n=250),[14] was 1600gms. Study conducted by Sunaina et al,[16] (n=225) 2004 shown weight on admission 1-1.5kg in 11.6%, 1.5-2kg in 23.4%, 2-2.5kg in 20.6%, 2.5-3kg in 17.5% and >3kg in 26.9%.

Comparative studies showing the sensitivity, specificity, positive predictive and negative predictive accuracy of various sepsis screening parametrs.

Comparative studies - total WBC count test

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1.	Zawar et al (17)	2003	82%	70%	--	--
3	Gerdes et a (13)	2004	100%	83%	27%	100 %
4	A.Narasimha (15)	2011	10.52%	91.66%	80%	24.44%
5	Present study	2011	77.78%	58.75%	21.21%	75%

The differences in the results of this parameter shown by the different studies may be due to variations in the blood sampling time, the severity of infection, the gestational age of the neonates, and the reduced sensitivity of this test in the first week of life.

Comparative studies – absolute neutrophil count (neutropenia)

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1.	Zawar et al (17)	2003	60%	74.5%	18.7 %	95%
2	Gerdes et a (13)	2004	38 to 96%	61 to 92%	20 - 77%	96-99%
4	A.Narasimha(15)	2011	89.47%	8.33%	75.55%	20
5	Present study	2011	87.5%	83.65%	51.03%	79.55%

These variations in the results shown by the different authors may be due to differences in the blood sampling time, the severity of infection, the gestational age of the neonates and the reduced sensitivity of this test in the first week of life.

Comparative studies - immature/total neutrophil ratio

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1	Zawar et al (17)	2003	60%	71.5%	17%	94.8 %
2	Gerdes et a (13)	2004	90-100%	30-78%	11-51%	99-100 %
3.	A.Narasimha(15)	2011	63.15%	75%	88.88%	39.13%
4.	Present study	2011	93.33%	30%	67.27%	94.12%

In the present study, Immature/Total neutrophil ratio > 0.2 was taken as one of the diagnostic screening criteria for detecting neonatal septicemia.

Comparative studies- degenrative change in neutrophils (toxic granulation and cytoplasmic vacuolations)

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1.	A.Narasimha(15)	2011	68.42%	66.66%	66.66%	40 %
2.	Present study	2011	88%	90.62%	72%	96 %

Comparative studies: platelet count (thrombocytopenia)

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1.	A.Narasimha(15)	2011	47.36%	75%	85.71%	31 %
2.	Present study	2011	93.33	25	25.92	93.02

Comparative studies – micro ESR

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1	Mishra et al (19)	1989	62%	88%	-	-
2	K K Diwakar (20)	1999	62.5%	60.9%	38.4 %	80.6 %
3.	Walliullah SM (21)	2010	63.3%	60.0%	-	-
4.	Present study	2011	64.44%	51.25%	20.41 %	76.64 %

In the present study, a micro-Erythrocyte sedimentation rate value > 15mm at the end of 1st hour was taken as the diagnostic screening criteria

for detecting neonatal septicemia. It has a sensitivity of 64.44% which is comparable with other studies. These variations in the results shown by the different authors may be due to method of estimations of Erythrocyte sedimentation rate and the sample size.

Comparative studies - C-reactive protein

SL N	Author	Year	Sensitivity	Specificity	PPV	NPV
1.	Nuntnarumit P(22)	2002	100%	94%	91.6 %	100 %
2.	Varsha et al (23)	2003	60%	88.2%	33%	95.7 %
3.	Gerdes et al (13)	2004	70%-93%	78%-94%	7%-43%	97-99 %
4.	Present study	2011	91.45%	85%	22.05 %	86%

In the present study C-Reactive protein value has sensitivity of 91.45% & negative predictive value of 86% which is comparable to observation made by other authors. The difference in various studies is due to different cut-off value used in the qualitative test (kit). We had higher sensitivity because our cut-off was 6 µg/ml.

CONCLUSION

- Absolute neutrophil count has 87.5% sensitivity, 83.65% specificity, 51.03% PPV and 79.5% NPV. Total white blood count has 77.5% sensitivity, 58.75% specificity, 21.21% PPV and 75% NPV. Immature /Total neutrophil ratio >0.20 has a 93.33% sensitivity, 30% specificity, 67.27% PPV and 94.12% NPV. Immature /Total neutrophil ratio >0.4 has 98.25% sensitivity, 93.75% specificity, 60% PPV and 83.33% NPV. Toxic granules and cytoplasmic vacuoles in neutrophils has 88% sensitivity ,90.62% specificity,72% PPV and 96% NPV.
- Platelet count has 93.33% sensitivity, 25% specificity, 25.92% PPV and 93.02% NPV.
- C-Reactive Protein has 91.45% sensitivity, 85% specificity, 22.05% PPV and 86% NPV.
- Micro Erythrocyte Sedimentation Rate has 64.44% sensitivity, 51.25% specificity, 20.41% PPV and 76.64% NPV.

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