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A Cross-Sectional Study of Blood Glucose Levels in Neonatal Sepsis and its Outcome in a Tertiary Care Hospital, Davangere

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Abstract

Sepsis is an important cause of morbidity and mortality among neonates. Neonatal sepsis can alter the glucose level, and both hypoglycaemia and hyperglycaemia may occur. Hence the present study aimed to study the clinical profile of patients with neonatal sepsis and to correlate the blood sugar levels with different outcomes in neonatal sepsis patients. A cross-sectional study was conducted at Bapuji Child Health Institute and Research Institute attached to J.J.M. Medical College, Davangere. A total of 90 neonates under the age of 28 days old admitted to NICU with probable and culture-proven neonatal sepsis were included in the study. Glucose levels, complete blood count, CRP levels, septic screening, lumbar puncture, neurosonogram, urine culture, blood culture and sensitivity were analysed. Results revealed that GRBS scores were < 40 for 24 subjects, 41 to 100 for 39 subjects, 101 to 200 for 22 subjects and > 200 for 5 subjects. There were 57(63.3%) males and 33(36.7%) females in the clinically diagnosed cases of septicemia. Clinical presentation in sepsis showed that 82(91.1%) subjects were not feeding well, 19(21.1%) had convulsions, 51(56.7%) had fast breathing, 39(43.3%) had Severe chest indrawing, 25(27.8%) had a temperature, 43(47.8%) had a fever and 88(97.8%) had Decreased activity of admission. In Conclusion, alteration of glycaemic status occurred in septic newborns, and mortality was higher among septic newborns with altered glycaemic status.

Keywords: Neonatal sepsis; GRBS; Hypoglycaemia; Hyperglycaemia; Mortality

Introduction

Neonatal sepsis is one of the leading causes of morbidity and mortality among newborns, especially in the developing world.[(1)] More than half of the neonates admitted to the NICU carry a discharge diagnosis of probable sepsis. The signs and symptoms of neonatal sepsis are non-specific, and it carries a high risk of mortality (5-15%).[(2)]

The reported incidence of neonatal sepsis varies from 7 to 38 per 1000 live births in Asia, from 6.5 to 23 per 1000 live births in Africa, and from 3.5 to 8.9 per 1000 live births in South America and the Caribbean.[3,4] By comparison, rates reported in the United States and Australasia range from 1.5 to 3.5 per 1000 for early-onset sepsis (EOS) and up to 6 per 1000 live births for late-onset sepsis (LOS), a total of 6-9 per 1000 for neonatal sepsis, and 0.3-3 per 1000 live births in Europe.[5,6] A number of organisms are associated with neonatal sepsis such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, Group B Streptococcus (GBS), *Escherichia coli*, *Pseudomonas aeruginosa, Acinetobacter spp* and *Enterobacter spp* etc.[7] Gram-negative bacteria remain to be the major cause of neonatal sepsis in developing countries.[8,9]

A major proportion of the NICU inpatients receive antibiotics, either empirically or for proven sepsis. Definitive tests such as blood cultures are not rapid or particularly sensitive while screening tests such as white blood cells (WBC) counts and C- reactive protein (CRP) have at best a positive predictive value of about 40%.[2] Manifestations of neonatal sepsis include feeding problems, convulsions, lethargy, respiratory rates >60 breaths per minute, severe chest indrawing, axillary temperature >37.5°C or <35.5°C.[10,11]

A high or low blood glucose level may have a significant effect on the outcomes in patients of culture-proven and probable neonatal sepsis. The operational threshold for hypoglycaemia is defined as "that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature. This threshold is currently believed to be a blood glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).[12] Sepsis has been known to be the cause of 9.6% cases of neonatal hypoglycaemia.[13] A neonate having sepsis develops reluctance to feed contributing to hypoglycaemia. Similarly, increased metabolic demand and hypothermia accused by sepsis can bring down glucose levels.[14]

Hyperglycaemia is defined as a plasma glucose level of more than 145 mg/dl.[15] In neonatal sepsis, several neuroendocrine and inflammatory mediators are released, which causes hyperglycaemia. There is an increased production of stress hormones like glucagon, growth hormone, catecholamines, and glucocorticoids. These hormonal changes along with an increase in proinflammatory cytokines, i.e., interleukin 1,6 (IL-1, IL-6), and tumour necrosis factor (TNF)- alpha are important factors leading to hyperglycaemia.[16] Hence, considering this scenario, the current study studied the clinical profile of patients with neonatal sepsis and correlated the outcomes with blood sugar levels.

Materials and Methods

This was a cross-sectional study conducted for a period of two years, from Jan 2020 to Dec 2021. The main source of data for the study are the patients' proven sepsis, and lab reports suggested sepsis (probable sepsis) cases admitted to neonatal intensive care unit (NICU) with probable and culture-proven neonatal sepsis in Bapuji Child Health Institute and Research Institute attached to J.J.M. Medical College, Davangere.

Ninety neonates below the age of 28 days old were admitted to NICU with probable and culture-proven neonatal sepsis in Bapuji Child Health Institute and Research Institute attached to J.J.M. Medical College, Davangere were included in the study. The purpose of the study was explained to the neonates parents, and oral consent was taken. A pre-structured proforma was used to record the relevant information from individual neonates parents were selected for the study. The patients were included in the study based on the inclusion and exclusion criteria.

Glucose levels of all the neonates in the study were checked and recorded within 1 hour of admission through a glucometer using glucose oxidase strips by trained staff nurses. Venous blood samples of all the neonate patients were taken for complete blood count, c-reactive protein (CRP) levels for septic screening, blood culture and sensitivity. Urine samples of suspected urinary tract infection neonates were sent for a routine examination, culture, and sensitivity. Lumbar puncture was done in patients who showed signs and symptoms of meningitis to obtain cerebrospinal fluid for microscopic examination, protein, glucose levels and culture. Glucose levels were divided into four groups i.e., < 40 mg/dl, 40-100 mg/dl, 101-200 mg/dl and > 200 mg/dl. Patients were divided into two groups according to weight, i.e., < 2.5 kg and 2.5 kg.

Statistical Analysis

Data were entered in Microsoft Excel, and analysis was done using Statistical Software for Social Sciences (SPSS) version 20 (IBM SPASS statistics, IBM corp. released 2011). Data were represented in the form of percentages, frequencies and descriptive statistics (Mean and Standard deviation). Inferential statistics like chi-square were applied for qualitative data.

Results

A total of 90 subjects clinically diagnosed with neonatal sepsis were studied. Out of 90 (100%) subjects, 48 (53.3%) subjects were aged between 1 to 3 days, followed by 22 (24.4%) aged between 4 to 7 days. General random blood sugar (GRBS) scores were < 40 for 24 subjects, 41 to 100 for 39 subjects, 101 to 200 for 22 subjects and > 200 for 5 subjects. 18 (75%) subjects who were aged 1 to 3 days had GRBS scores <40, and 20 (51.3%) subjects had scores of 41 to 100. The Chi-square test showed a statistically significant association between age and GRBS scores (p=0.04) (Table 1). Males were predominantly higher, i.e., 57 (63.3%) as compared to females 33 (36.7%). Most of the females, i.e., 16 (41%) and 23 (59%) of males had GRBS scores of 41 to 100. There was a

statistically significant association between gender and GRBS scores (p=0.034). (Table 1) Early-onset sepsis (EOS) was seen in 51 (56.7%) subjects, whereas late-onset sepsis (LOS) was seen in 39 (43.3%) subjects. Culture proven (CP) was seen in 55 (61.1%) subjects, and probable sepsis (PS) was seen in 35 (38.9%) subjects. 18 (54.5%) females had LOS, whereas 36(63.2%) males had EOS. CP was higher in both males and females with 19 (57.6%) and 36 (63.2%), respectively. (Table 2)

Out of 6 (6.7%) inborn subjects, 3 subjects had GRBS scores of 41 to 100 and 4 (66.7%) subjects had EOS and CP sepsis. Similarly, out of 84 (93.3%) outborn subjects, 36 subjects had GRBS scores of 41 to 100, 47 (56%) subjects had EOS, and 51 (60.7%) had CP sepsis. Out of 52 (57.8%) lower segment cesarian section (LSCS) subjects, 23 subjects had GRBS scores of 41 to 100, 34 (65.4%) subjects had EOS, and 31 (59.6%) had CP sepsis. Similarly, out of 38 (42.2%) normal vaginal delivery (NVD) subjects, 16 subjects had GRBS scores of 41 to 100, 21 (55.3%) subjects had EOS, and 24 (63.2%) had CP sepsis. (Tables 1 and 2) The Chi-square test showed a statistically significant association between gestational age and EOS/LOS (p=0.005). Furthermore, there was also a statistically significant association between birth weight and EOS/LOS (p=0.041).

Out of 8 (8.9%) subjects without feeding difficulties, 4 subjects had GRBS scores of 41 to 100. Similarly, out of 82 (91.1%) subjects who had feeding difficulties, 35 subjects had GRBS scores of 41 to 100. Out of 71 (78.9%) subjects with a history of no convulsions, 34 subjects had GRBS scores of 41 to 100. Whereas, out of 19 (21.1%) subjects who had convulsions, 12 subjects had GRBS scores < 40. A statistically significant association between GRBS scores and convulsions was observed (p=0.001) (Table 2).

Out of 51 subjects having EOS, 44 (86.3%) subjects were not feeding well, 9 (17.6%) had convulsions, 37 (72.5%) had fast breathing, 30 (58.8%) had severe chest indrawing, 17 (33.3%) had a temperature, 15 (29.4%) had fever, 50 (98%) had decreased activity of admission. A statistically significant association was seen between sepsis and fast breathing (p=0.001), severe chest indrawing (p=0.001), and fever (p=0.00) (Table 3) and between CP/PS sepsis and fast breathing (p=0.011), severe chest indrawing (p=0.007), temperature (p=0.023).

The mean weight of the study subjects having GRBS scores of 101 to 200 was 2.27 ± 0.72 kg. Mean length was slightly higher – 48.4 ± 7.5 cm for subjects having GRBS scores >200. Head circumference was higher for subjects having GRBS scores of 101 to 200 (33.27 ± 1.93). Heart rate (172 ± 11.49) and respiratory rate (64.80 ± 7.56) were higher for subjects with GRBS scores > 200. (Table 4) Peripheral pulse was feeble among 26 (28.9%) subjects and well felt among 64 (71.1%) subjects. Cardiac resynchronization therapy (CRT) was <3 among 65 (72.2%) subjects and > 3 among 25 (27.8%) subjects. The temperature was febrile among 38 (42.2%) subjects, hypothermic among 26 (28.95) subjects and normal among 26 (28.9%) subjects. There was a statistically significant association between GRBS scores and peripheral pulse (p=0.031), CRT (p=0.011) and temperature (p=0.044).

The mean Hb (14.38 ± 3.36), RBC (4.24 ± 0.86), and hematocrit % (HCT) (41.29 ± 10.13) were lower among study subjects having GRBS scores of 101 to 200. Mean TC (14888 ± 12080.85) and platelets (70200 ± 50420.23) were lower in subjects having GRBS scores >200. CRP levels were lower (59.75 ± 57.24) in subjects having GRBS scores <40. (Table 4) The mean hospital stay was higher in subjects having GRBS scores of 101 to 200 days (10.68 ± 9.74), followed by subjects having <40 GRBS scores (10.13 ± 7.17). Mean Hb (15.41 ± 3.68), RBC (4.54 ± 1.14), TC (20642.74 ± 11847.72), HCT% (45.33 ± 11.10) and platelets (89225.64 ± 68082.35) were lower in study subjects having LOS sepsis. CRP levels were found to be higher in subjects having LOS sepsis- 94.59 ± 77.97. Mean Hb (16.65 ± 3.57), TC (21243.11 ± 12458.93), HCT% (48.12 ± 10.48), and platelets (88618.18 ± 58338.89) were lower in subjects having CP sepsis. RBC (4.76 ± 0.86) and CRP levels- 54.61 ± 55.42 were lower in subjects having PS sepsis.

Among 25 (27.8%) subjects who died, 9 (23.1%) had GRBS scoring of 41 to 100, and 8 (36.4%) subjects had GRBS scoring of 101 to 200. There was a statistically significant association between GRBS scores and outcome (p=0.023). Out of those subjects, 17 (68%) had EOS, 8 (32%) had LOS sepsis, 20 (80%) had CP sepsis, and 5 (20%) had PS sepsis. There was a statistically significant association between outcome and CP/PS sepsis (p=0.023) (Table 5).

Discussion

In this study, it was observed that the majority of the study subjects were aged between 1 to 3 days. The GRBS scores of 24 subjects were below 40. the levels between 41 to 100 were observed for 39 subjects; for 22 subjects, the glucose level was between 101 and 200, and 5 subjects had glucose levels above 200. Most subjects belonged to the age group of 1 to 3 days with a GRBS score below 40. A study by Ahmed and Khalid observed that the glucose levels of 50 patients (9.9%) were below 40 mg/dl. These levels were between 40 mg/dl and 100 mg/dl for 322 patients (64.1%), for 95 patients (18.9%) the level was between 101 mg/dl and 200 mg/dl, and 35 patients (6.9%) had glucose level above 200 mg/dl.[14] In another study reported by Begum et al. observed hyperglycemia in 4.62% of their study patients.[16] A neonate having sepsis develops reluctance to take feed, and this can lead to hypoglycemia. Similarly, increased metabolic demand and hypothermia caused by sepsis can bring down the glucose level.

In the present study, there were 57 (63.3%) male subjects, and 16 (41%) subjects were female, showing males were

Table 1. Association of GRBS with age, gender, delivery details and mode of delivery

Age	GRBS (groups)				Chi square test
	< 40	41 to 100	101 to 200	> 200	
1- 3 days	18(75.0%)	20(51.3%)	7(31.8%)	3(60.0%)	test value 21.57 p value 0.04
4-7 days	5(20.8%)	9(23.1%)	7(31.8%)	1(20.0%)	
11- 14 days	1(4.2%)	4(10.3%)	2(9.1%)	0(0.0%)	
15 to 21 days	0(0.0%)	5(12.8%)	1(4.5%)	1(20.0%)	
21 to 28 days	0(0.0%)	1(2.6%)	5(22.7%)	0(0.0%)	
Gender	**GRBS (groups)**				**Chi square test**
	< 40	**41 to 100**	**101 to 200**	**> 200**	
Females	9(37.5%)	16(41.0%)	5(22.7%)	3(60.0%)	test value 3.33 p value 0.034
Males	15(62.5%)	23(59.0%)	17(77.3%)	2(40.0%)	
Delivery Details	**GRBS (groups)**				**Chi square test**
	< 40	**41 to 100**	**101 to 200**	**> 200**	
Inborn	2(8.3%)	3(7.7%)	0(0.0%)	1(20.0%)	test value 3.17 p value 0.36
Out born	22(91.7%)	36(92.3%)	22(100.0%)	4(80.0%)	
Mode of Delivery	**GRBS (groups)**				**Chi square test**
	< 40	**41 to 100**	**101 to 200**	**> 200**	
LSCS	16(66.7%)	23(59.0%)	11(50.0%)	2(40.0%)	test value 1.99 p value 0.57
NVD	8(33.3%)	16(41.0%)	11(50.0%)	3(60.0%)	

Table 2. Association of sepsis with gender, delivery details and mode of delivery

Sepsis	Gender		Total	Chi-square test
	Females	**Males**		
EOS	15(45.5%)	36(63.2%)	51(56.7%)	Test value 2.66 p value 0.102
LOS	18(54.5%)	21(36.8%)	39(43.3%)	
CP	19(57.6%)	36(63.2%)	55(61.1%)	Test value 0.27 p value 0.6
PS	14(42.4%)	21(36.8%)	35(38.9%)	
Sepsis	**Delivery Details**		**Total**	**Chi-square test**
	Inborn	**Out born**		
EOS	4(66.7%)	47(56.0%)	51(56.7%)	Test value 0.26 p value 0.609
LOS	2(33.3%)	37(44.0%)	39(43.3%)	
CP	4(66.7%)	51(60.7%)	55(61.1%)	Test value 0.08 p value 0.77
PS	2(33.3%)	33(39.3%)	35(38.9%)	
Sepsis	**Mode of Delivery**		**Total**	**Chi-square test**
	LSCS	**NVD**		
EOS	34(65.4%)	17(44.7%)	51(56.7%)	Test value 3.81 p value 0.051
LOS	18(34.6%)	21(55.3%)	39(43.3%)	
CP	31(59.6%)	24(63.2%)	55(61.1%)	Test value 0.11 p value 0.73
PS	21(40.4%)	14(36.8%)	35(38.9%)	

Table 3. Association of early onset/late-onset sepsis with clinical presentation

Clinical presentation in Sepsis		SEPSIS		Total	Chi-square test
		EOS	LOS		
Not feeding well	No	7(13.7%)	1(2.6%)	8(8.9%)	**Test value 3.39 p value 0.065**
	Yes	44(86.3%)	38(97.4%)	82(91.1%)	
Convulsions	No	42(82.4%)	29(74.4%)	71(78.9%)	**Test value 0.84 p value 0.35**
	Yes	9(17.6%)	10(25.6%)	19(21.1%)	
Fast breathing	No	14(27.5%)	25(64.1%)	39(43.3%)	**Test value 12.09 p value 0.001**
	Yes	37(72.5%)	14(35.9%)	51(56.7%)	
Severe chest indrawing	No	21(41.2%)	30(76.9%)	51(56.7%)	**Test value 11.5 p value 0.001**
	Yes	30(58.8%)	9(23.1%)	39(43.3%)	
Temperature	No	34(66.7%)	31(79.5%)	65(72.2%)	**Test value 1.81 p value 0.17**
	Yes	17(33.3%)	8(20.5%)	25(27.8%)	
Fever	No	36(70.6%)	11(28.2%)	47(52.2%)	**Test value 15.91 p value 0.00**
	Yes	15(29.4%)	28(71.8%)	43(47.8%)	
Decreased activity of admission	No	1(2.0%)	1(2.6%)	2(2.2%)	**Test value 0.037 p value 0.84**
	Yes	50(98.0%)	38(97.4%)	88(97.8%)	

Table 4. Association of GRBS with anthropometric values, heart and respiratory rates and lab investigations

		N	Minimum	Maximum	Mean	SD
Weight (kg)	101 to 200	22	1.10	3.90	2.27	0.72
Length (cm)	> 200	5	40.0	60.0	48.40	7.50
Head Circumference	101 to 200	22	29.0	35.0	33.27	1.93
		N	**Minimum**	**Maximum**	**Mean**	**SD**
HR	>200	5	158.0	188.0	172.00	11.49
RR	> 200	5	56.0	76.0	64.80	7.56
		N	**Minimum**	**Maximum**	**Mean**	**SD**
HB	101 to 200	22	7.7	19.8	14.38	3.36
RBC (m/cumm)	101 to 200	22	2.40	5.60	4.24	0.86
TC (cells/cumm)	> 200	5	3950.0	32240.0	14888.00	12080.85
HCT (%)	101 to 200	22	22.2	57.0	41.29	10.13
Platelet (lakhs/cumm)	> 200	5	16000.0	127000.0	70200.00	50420.23
CRP (mg/l)	< 40	24	15.0	250.8	59.75	57.24

Table 5. Association of sepsis, culture proven (cp) / probable sepsis (ps) with outcome

		Outcome		Total	Chi-square test
		Death	Discharged		
Sepsis	EOS	17(68.0%)	34(52.3%)	51(56.7%)	**Test value 1.81 p value 0.17**
	LOS	8(32.0%)	31(47.7%)	39(43.3%)	
Culture proven (CP) / probable sepsis (PS)	CP	20(80.0%)	35(53.8%)	55(61.1%)	**Test value 5.19 p value 0.023**
	PS	5(20.0%)	30(46.2%)	35(38.9%)	

predominantly higher. Similar findings were observed by Gupta et al., i.e., 157 (71.4%) were males, and 63 (47.3%) were females, which are comparable with the present study.[17] Early-onset sepsis and late sepsis were seen in 51 (56.7%) and 39(43.3%) subjects in the present study. Culture proven was seen in 55 (61.1%) subjects, and most of the females had late-onset sepsis, whereas males had early-onset sepsis. A study by Ellahony et al. showed EOS in 45(25.8%), and LOS in 129(74.1%), and proven sepsis was found in 101 (58%) of the study subjects.[18]

In the current study, the incidence of suspected EOS for inborn and outborn subjects was 4/6 admission and 47/84 admission. Among subjects of suspected LOS for inborn and outborn subjects were 2/6 admissions and 37/84 admissions. Culture proven sepsis was 4/6 in inborn admissions and 51/84 in outborn admissions. Probable sepsis was seen in 2/6 of inborn and 33/84 in outborn admissions. A study conducted by Jajoo et al. reported the incidence of suspected EOS for outborn subjects as 190/1000 admissions. However, sepsis screen and culture were positive in 57% and 18 % (n+15) of suspected EOS, respectively, in their study.[19]

The majority of the subjects had feeding difficulties and convulsions, with a GRBS score of less than 40 was observed in our study. Many different neonatal groups are at risk of developing low blood glucose concentrations. For example, preterm baby, large for gestational age, infant of a diabetic mother, intrauterine growth restriction (IUGR), sepsis, shock, asphyxia, hypothermia, respiratory distress syndrome (RDS).[15] Sepsis has been known to be the cause of 9.6% of cases of neonatal hypoglycemia.[13] A neonate having sepsis develops reluctance to feed, and this can lead to hypoglycemia. Similarly, increased metabolic demand and hypothermia caused by sepsis can bring down the glucose level.[14] Severe and prolonged neonatal hypoglycemia are associated with a risk of long term neurodevelopmental sequelae like microcephaly, epilepsy, visual impairment and long-term disability. Persistent hypoglycemia leads to irreversible cellular dysfunction, organ failure and eventually death.

The clinical features of neonatal sepsis are not feeding well, convulsions, fast breathing (>60 breath/min on the second count), severe chest indrawing, low body temperature (less than 35.5°C or 95.9°F), fever (more than 37.5°C or 99.5°F)[20] and movement only when stimulated or no movement at all. In the present study, among 39 (43.3%) subjects who had severe chest indrawing, 16 subjects had GRBS of 41 to 100. Similarly, out of 43 (47.8%) subjects who had a fever, 21 subjects had GRBS scores of 41 to 100 were observed. 21(53.8%) out of 43 subjects had fever with a GRBS score of 41 to 100. Clinical presentation in sepsis showed that 82(91.1%) subjects were not feeding well, 19(21.1%) had convulsions, 51(56.7%) had fast breathing, 39(43.3%) had severe chest indrawing, 25(27.8%) had a temperature and 43(47.8%) had a fever. In the study of Tripathi et al. 7 (13.3%) of the culture-proven sepsis, subjects had a fever. In the present study, among 24 (100%) subjects with below 40mg/dL of GRBS, 13 subjects (54.2%) had fast breathing, which is higher when compared to the study of Tripathi et al., wherein 2 (9.5%) subjects had birth asphyxia.[21]

Among 25 (27.8%) study subjects who died, 23.1% had GRBS score of 41 to 100 and 36.4% subjects had GRBS scores of 101 to 200. The findings of the present study showed an association between glucose levels and outcome of mortality, between CP/PS sepsis and outcome. The majority of the associated complications were disseminated intravascular coagulation, respiratory distress syndrome (RDS), and multiorgan dysfunction syndrome.

Conclusions

Our study identified birth weight, neonatal age, meconium, the reason for cesarian section (CS), and the duration of stay on admission among CS deliveries as risk factors significantly associated with neonatal sepsis. Clinical presentation in sepsis showed that subjects were not feeding well, had convulsions, fast breathing, severe chest indrawing, temperature, fever and decreased activity of admission. GRBS score and convulsion, CP/PS sepsis and fast breathing, severe chest indrawing, and temperature were found to be significantly associated. Therefore, through the study outcomes, it was concluded that neonatal hypoglycaemia and hyperglycaemia are associated with the overall mortality in neonatal sepsis.

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