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Original Research Article

Neurodevelopmental Outcome in Neonatal Sepsis with Hypoglycemia: A Prospective Cohort Study

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Abstract:

Background: Neonatal sepsis and neonatal hypoglycemia are risk factors for abnormal neuro-motor and cognitive development and has been associated with abnormalities on brain imaging and a spectrum of developmental delays.

Objectives: Aim of this study to determine the impact of Neonatal sepsis and hypoglycemia on neonatal neuro-developmental outcomes in our tertiary care hospital.

Methods: This was a cross sectional observational study enrolled neonates suspected of neonatal sepsis and hypoglycemia admitted in our hospital during the study period. The neonatal hypoglycemia was defined as blood glucose ≤45mg/dL. Growth and Neuro-developmental Outcomes was measured and depicted in terms of weight, length, head circumference, Cerebral Palsy (CP), Visual Impairment, Hearing Impairment, developmental delay, tone abnormalities and retinopathy of Prematurity.

Results: Among hypoglycemia group 32 (64%) were boys whereas among control group 56% had boys. No significant difference of baseline variables of neonatal hypoglycemia and control group, except Apgar score at 1 min and Hypoglycemic episodes. Among maternal demographic data Gestational age were significantly differ between the hypoglycemia and non hypoglycemic group. Majority of the maternal and neonatal parameters such as gestational age, Maternal Diabetes, IUGR, hospital stay, Neonatal Hypoglycemia, birth weight, Birth length and neonatal OFC were significantly difference among sepsis and non-sepsis group. Comparing the outcomes between the two groups the outcome of abnormal neurological examination was significantly more in sepsis group than in control.

Conclusion: Neonatal sepsis was significantly associated with the abnormal neuro developmental outcomes but neonatal hypoglycemia produced neuro-developmental delay but it was not statistically significantly associated.

Keywords: Neonates, Sepsis, Neonatal Hypoglycemia, Neuro-Developmental Outcomes.

Introduction

Neonatal hypoglycemia refers to the temporary condition of a decreased blood sugar level in a neonate, which is especially likely to occur in the newborns of diabetic mothers [1].

Neonates who are born from mothers with diabetes have an average rate of hypoglycemia of 8–30%, which is significantly higher than that of infants who are born from nondiabetic women (3%) [2].

With the improvement of living standards and lifestyle changes, the incidence of gestational diabetes mellitus has been increasing in recent years [3, 4]. Therefore, neonatal hypoglycemia is more frequent today than in the past. Hypoglycemia is still a major metabolic abnormality in neonates [2].Neonatal hypoglycemia is a common and readily treatable risk factor for neurologic impairment in children.

Although associations between prolonged symptomatic neonatal hypoglycemia and brain injury are well established, [5] the effect of milder hypoglycemia on neurologic development is uncertain [6].

Consequently, large numbers of newborns are screened and treated for low blood glucose concentrations, which involves heel-stick blood tests, substantial costs, and the possibility of

iatrogenic harm. Under current guidelines,[7] up to 30% of neonates are considered to be at risk for hypoglycemia, 15% receive a diagnosis of hypoglycemia, and approximately 10% require admission to a neonatal intensive care unit,[8] costing an estimated $2.1 billion annually in the United States alone[9].In year 2010, 15 million infants were born preterm worldwide.

Out of these, 13 million were survived and 2.7% had moderate-to-severe neurodevelopment impairment [10]. Intrauterine infections are also associated with cerebral white matter injury and subsequent neurodevelopmental impairment [11]. The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. Septicemia was the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births.

Many LBW and ELBW infants have at least 1 episode of early-onset or late-onset infection during their initial hospital stay. Neonatal infections and necrotizing enterocolitis (NEC) have been linked with an increased risk of neurodevelopment impairment in LBW survivors [12]. However, the prognostic importance of infection relative to the other neonatal morbidities remains uncertain.

Materials and Methods

This was a cross sectional observational carried out in the department of pediatrics in a tertiary care hospital in central India. All neonates admitted in our hospital during the study period were enrolled.

Neonatal sepsis was considered in the presence of positive blood culture and/or clinical and laboratory sign suggest of infection.

The neonatal hypoglycemia was defined as blood glucose ≤45mg/dL. These were then further subdivided by glucose ranges into degree of severity, with most severe defined as glucose ≤35 mg/dL, moderate hypoglycemia defined as glucose level of 36 to 40 mg/dl, and mild defined as glucose level of 41 to 45 mg/dl

Inclusion criteria

- Neonates age < 1 years with both sexes
- Neonates diagnosed as sepsis and hypoglycemic
- Whose parents or guardians provide written inform consent

Exclusion criteria

- Age more than one year
- Infant of congenital malformation or genetic disorder
- Infants with major congenital malformations, severe perinatal asphyxia (5min Apgar < 4 and/or cord Ph < 7.0), and post neonatal meningitis or other CNS infections
- Whose parents or guardians not provide consent for the study

Gestational age was determined by first-trimester ultrasound scan. Relevant neonatal data of all neonates including morbidity and mortality during the hospital stay was recorded in a predesigned proforma at the time of discharge from the hospital. Recorded data included birth weight, sex, and the need for resuscitation at birth and Apgar scores at 1 and 5 minutes

Socio-demographic data were recorded from all the participants included history, breast feeding status, clinical examination and laboratory investigation was done.

Growth is measured and depicted in terms of weight, length, and head circumference.

Neuro-developmental Outcomes was measured in the form of Cerebral Palsy (CP), Visual Impairment, Hearing Impairment, Developmental Delay, Tone Abnormalities, Osteopenia of Prematurity, Hyper reactive Airway Disease and Hospital Readmissions during Infancy.

Statistical Analysis: Analysis was performed with SAS software, version 22. Results are presented as risk ratios and mean differences with 95% confidence intervals. A two-tailed alpha level of less than 0.05 was considered to indicate statistical significance

Results

This study enrolled 50 children diagnosed as neonatal hypoglycemia and 50 aged matched healthy siblings without neonatal hypoglycemia.

Among hypoglycemia group 32 (64%) were boys and 18 (36%) were girls whereas among control group 56% had boys and 44% have girls.

No significant difference of baseline variables of neonatal hypoglycemia and control group, except Apgar score at 1 min and Hypoglycemic episodes was significantly differ between the groups ($P<0.05$).

Among maternal demographic data Gestational age were significantly differ between the hypoglycemia and non hypoglycemic group [Table: 1].

Table 1: Maternal and Neonatal Demographics and Confounding Variables with and without hypoglycemia

Variables	Hypoglycemia group N=50	Control group N=50	P value
Baseline variables of the neonatal data			
Boys / Girls	32/ 18	28/22	0.414
Birth weight (g)	3024±751	3139±837	0.471
Cord pH	7.1±0.4	7.2±0.5	0.272
Apgar at 1 min	8.6±1.2	9.2±1.6	**0.036**
Apgar at 5 min	9.4±1.1	9.7±1.3	0.215
Hypoglycemic episodes	1.8±0.7	0	**<0.001**
Sepsis	22 (44%)	12 (24%)	>0.05
Baseline variables of the maternal data			
Gestational age (wks + days)	37.2± 1.5	38.06 ± 1.8	**0.010**
Maternal diabetes	27 (54%)	17 (34%)	0.840
Preterm labor	29 (58%)	21 (42%)	
IUGR	10 (20%)	6 (12%)	
Caesarian section	42 (84%)	39 (78%)	
Premature rupture of membrane	12 (24%)	9 (18%)	

Most of the neonates have mild hypoglycemia (43%) followed by moderate hypoglycemia (34%) then severe hypoglycemia (23%) [Figure 1].

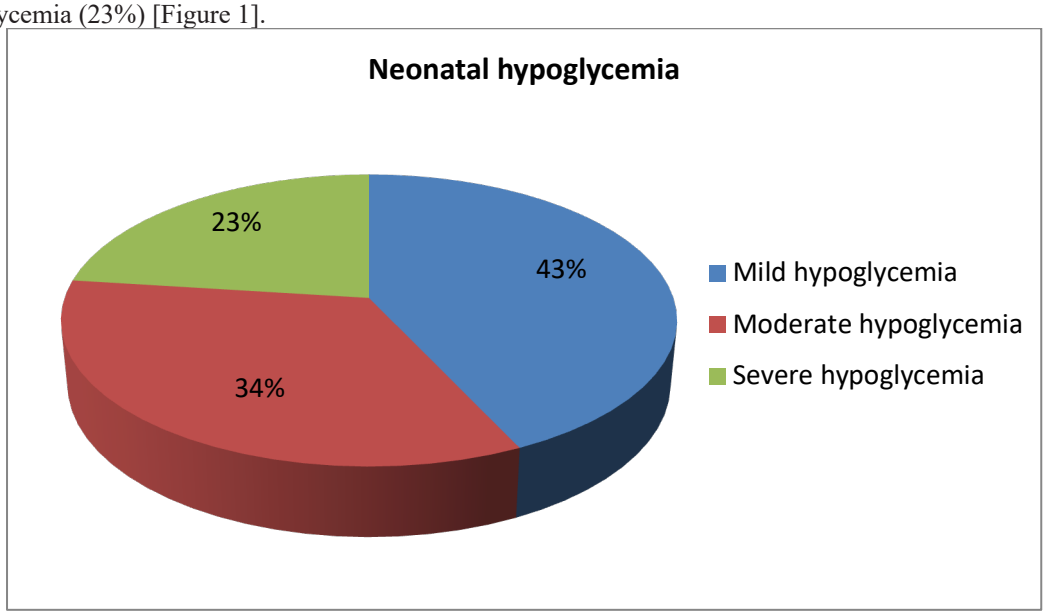

Figure 1: Severity of hypoglycemia among the neonatal subjects

Among the total participants 46 infants had sepsis and 54 infants were without sepsis as control group. On comparing the sepsis and non-sepsis group the sex ratio were similar in both the group. Majority of the maternal and neonatal parameters such as gestational age, Maternal Diabetes, IUGR, hospital stay, Neonatal Hypoglycemia, birth weight, Birth length and neonatal OFC were significantly difference among sepsis and non-sepsis group [table:2].

Table 2: Comparison of basic variables between neonatal sepsis and non-sepsis groups

Characteristics	Sepsis group N=46	No sepsis group N=54	P value
Boys / Girls	30/ 16	34/20	0.814
Birth weight, median (gms)	2708	3065	**<0.05**
Birth OFC, median (cm)	26.87	29.54	**<0.05**
Birth length, median (cm)	36.44	38.78	**<0.05**
Gestational age (wks)	35.4± 2.5	37.7 ± 2.8	**<0.001**
Neonatal Hypoglycemia	41 (89.2%)	9 (16.7%)	**0.016**
Maternal Diabetes	10 (21.7%)	8 (14.8%)	
IUGR	11 (23.9%)	10 (18.5%)	
Hospital stay, Mean ± SD	16.4± 4.5	12.7 ± 2.3	**<0.05**

Comparing the outcomes between the two groups the outcome of abnormal neurological examination was significantly more in sepsis group than in control group ($p < 0.05$).

Table 3: Neuro developmental outcomes in neonatal sepsis and non-sepsis groups

Neuro developmental outcomes	Sepsis group	No sepsis group	P value
Abnormal outcome	69.6%	20.4%	**<0.001**
Cerebral palsy	13.1%	3.7%	0.10
Squint	8.6%	5.6%	0.68
Hearing aids	6.5%	1.8%	0.17
DDST fail	32.6%	9.3%	**0.001**
Blindness	10.8%	00%	**0.01**
Tone abnormalities	13.1%	1.8%	0.081
Abnormal BERA	26.1%	5.6%	**<0.001**
Retinopathy of Prematurity	23.9%	9.3%	**0.001**
Abnormal Neuro-sonogram	60.8%	11.1%	**0.001**

Discussion

Many observational studies have demonstrated neuro developmental impairment and/or abnormal MRI scan of the brain after neonatal hypoglycemia, depending on the severity, duration, and co morbid factors. High-evidence clinical studies on the cerebral outcome after neonatal transient hypoglycemia are sparse [13].

In our study most of the infant's participants were boys; similar finding also reported by others studies: Harris DL, et al [14] and McKinlay, et al [15]. Present study showed that neonates with sepsis had a significantly higher incidence of abnormal neuro developmental outcomes than neonates without sepsis, our results were comparable with the Manikyamba et al [16] and Sunil J, et al [17].

A study done by M. Modi, et al [18], reported that very low birth weight (VLBW) infants exposed to culture-proven sepsis comparing poor neuro developmental outcomes than VLBW infants without sepsis. Our study showed that infants with the sepsis were significantly growth retarded as compared to control group; in agreement with the Stoll et al [19], demonstrates that infection affects weight and head circumference at both 36 weeks of PCA and 18 to 22 months of corrected gestational age.

A study performed by Soleimani et al. [20], observed that premature infants are at risk of major and minor deficits such as cerebral palsy, cognitive and speech delays, motor and visual deficits, psychosocial and behavioral disorders and dysfunction at school.

Current study reported that Neonatal hypoglycemia was not significantly associated with an increased risk of neuro developmental impairment, consistent observation found in many other research studies like;' Rasmussen, et al [21] and Goode RH, et al [22], in contrast to our study Boluyt N, et al [23] reported that significant neuro developmental impairment and/or abnormal MRI scan of the brain was seen after neonatal hypoglycemia. The low-threshold group had more episodes of recurrent and of severe hypoglycemia, which impact may only become overt after a longer follow-up time.

We were not able to establish an association between the degree of hypoglycemia and neurologic outcomes, most likely because treatment was effective and the infants were monitored closely, so that recurrent or severe hypoglycemia was rare.

Conclusion

We have concluded that the Neonatal sepsis were significantly associated with abnormal neuro developmental outcomes (both cognitive and psychomotor) in neonates. Neonatal hypoglycemia produced neuro-developmental delay but it was not statistically significantly associated.

References

1. Stanley CA, Baker L. The causes of neonatal hypoglycemia. N Engl J Med. 1999; 340:1200–1.
2. Alemu BT, Olayinka O, Baydoun HA, Hoch M, Elci MA. Neonatal hypoglycemia in diabetic mothers: a systematic review. CurrPediatr Res. 2017; 21:42–53.
3. Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG. 2017; 124:804–13.
4. Huhn EA, Massaro N, Streckeisen S, Manegold-Brauer G, Schoetzau A, Schulzke SM, et al. Fourfold increase in prevalence of gestational diabetes mellitus after adoption of the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. J Perinat Med. 2017; 45:359–66.
5. Burns CM, Rutherford MA, Boardman JP, and Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008; 122:65–74.
6. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics. 2006; 117:2231–43.

7. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011; 127:575–9.
8. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr. 2012; 161:787–91.
9. March of Dimes Perinatal Data Center. Special care nursery admissions. 2011. http://www.marchofdimes.org/peristats/pdfdocs/nicu_summary_final.pdf
10. G. R. Robaina Castellanos and S. D. L. C. Riesgo Rodrıguez, "Neonatal sepsis and neurodevelopment in very low birth weight infants in Matanzas, Cuba 2006-2010: a prospective cohort study," Medwave, vol. 16, no. 3, p. e6422, 2016.
11. K. B. Nelson andR.E.Willoughby, "Overview: Infection during pregnancy and neurologic outcome in the child," Mental Retardationand Developmental Disabilities Research Reviews, vol. 8, no. 1, pp. 1-2, 2002.
12. S. Chaudhari, M. Otiv, B. Khairnar, A. Pandit, M.Hoge, and M. Sayyad, "Pune low birth weight study - Growth from birth to adulthood," Indian Pediatrics, vol. 49, no. 9, pp. 727–732, 2012.
13. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF (2012) Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 130:e265–e272
14. Harris DL, Weston PJ, Harding JE. Lactate, rather than ketones, may provide alternative cerebral fuel in hypoglycaemic newborns. Arch Dis Child Fetal Neonatal Ed 2015; 100: F161-F164.
15. McKinlay CJ, Alsweiler JM, Ansell JM, et al; CHYLD Study Group. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med. 2015;373(16):1507–1518
16. D.Manikyamba, N.Madhavi, A.Krishna Prasadetal.,"Anitha, Morbidity and Mortality Profile of LBW Babies and Their Growth and Neurodevelopment Outcome at 1 year-NICU," Scholars Journal of Applied Medical Sciences, vol. 3, no. 4B, pp. 1721–1725,2015
17. Sunil J. Pawar, Tejopratap Oleti, Siluvery Bharathi, Shyam sunder Tipparaju, and Ershad Mustafa, Growth and Neurodevelopmental Outcome in Preterm LBW Infants with Sepsis in India: A Prospective Cohort, Hindawi International Journal of Pediatrics Volume 2018, Article ID 5735632, 9 pages
18. M. Modi, S. Saluja, N. Kler et al., "Growth and neuro developmental outcome of VLBW infants at 1 year corrected age, "Indian Pediatrics,vol.50,no.6,pp.573–577,2013
19. Dusick, B. R. Vohr, J. Steichen, L. L. Wright, L. Mele, and J. Verter, "Factors affecting growth outcome at 18 months in extremely low birth weight (ELBW) infants,"Pediatric Research,vol.43,article213A,1998.
20. F. Soleimani, F. Zaheri, and F. Abdi, "Long-term neuro developmental outcomes after preterm birth," Iranian Red Crescent Medical Journal, vol.16,no. 6,Article IDe 17965, 2014
21. Annett Helleskov Rasmussen & Sonja Wehberg & Fani Pørtner & Anna-Marie Larsen & Karen Filipsen & Henrik Thybo Christesen, Neuro developmental outcomes after moderate to severe neonatal hypoglycemia, European Journal of Pediatrics (2020) 179:1981–1991
22. Goode RH, Rettiganti M, Li J, et al. Developmental Outcomes of Preterm Infants with Neonatal Hypoglycemia. Pediatrics. 2016; 138(6):e20161424
23. Boluyt N, van Kempen A, Offringa M (2006) Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics 117:2231–2243