



ASSOCIATION OF NEUREGULIN 1 LEVELS, MATERNAL AND NEONATAL RISK FACTORS WITH BLOOD GLUCOSE LEVELS IN PRETERM INFANTS

Bugis Mardina Lubis

Department of Pediatric, University of Sumatera Utara, Medan, Indonesia

ABSTRACT

Background : Prematurity remains as the most common cause of morbidity and mortality in neonatal period.

Maternal and neonatal risk factors associated with prematurity had been identified before. Neuregulin (NRG) 1 plays important role in the development of lungs, heart and brain of the infants. Preterm infants are vulnerable population to develop problems due to disturbance in NRG 1 gene expression, which associated to various condition. The association between NRG 1 levels and blood glucose levels in preterm infants remains unclear.

Objective : To determine the association of NRG 1 levels, maternal and neonatal risk factors with blood glucose levels in preterm infants.

Design and Methodology : A cross-sectional study on 50 consecutive preterm infants on hospitals in Medan, Indonesia from June to August 2018. Maternal and neonatal risk factors were recorded. Blood glucose levels were obtained from venous blood sample and were checked serially from the time of delivery within the first hour of life until discharged from hospital or 72 hours of age. Univariate and bivariate (Chi square and Fisher exact test) analysis were performed with 95% CI and P value <0.05 were considered statistically significant.

Result : Out of 50 preterm infants, 13 infants had hypoglycemia (26%). There was no association between maternal risk factors with hypoglycemia. Regarding neonatal risk factors, birth weight of ≤ 2500 gr and gestational age of 32–<35 weeks were associated with hypoglycemia (P=0.010 and P=0.021, respectively). NRG 1 levels had median of 180,6 pg/mL. Preterm infants who developed hypoglycemia had lower NRG levels compared to their counterparts (P=0.010). Significant associated risk factors to hypoglycemia was NRG 1 levels, whereas low NRG 1 levels (<181 pg/mL) had higher risk to develop hypoglycemia (P=0.035; OR=4.86 (95% CI=1.11–21.16).

Conclusion : Preterm infants with low NRG 1 levels have higher risk to develop hypoglycemia.

KEYWORDS : Preterm infants, neuregulin 1, maternal and neonatal risk factors, hypoglycemia

INTRODUCTION

Prematurity is one of the highest causes of perinatal death in addition to low birth weight (LBW) infants, asphyxia or respiratory disorders. The biggest challenge is how to reduce the risk of morbidity which will reduce neurological disorders and long-term growth and development disorders so that these preterm infants can grow optimally.¹

One of the most common morbidity in premature infants is hypoglycemia. The immaturity of the glucose formation system, inadequate energy storage, and hyperinsulinism conditions can affect the occurrence of hypoglycemia in preterm infants.²

Symptoms of hypoglycemia in infants include jitteriness, convulsions, hypotonia, coma, refusal to feed, cyanosis, high pitched cry, hypothermia and even asymptomatic in most cases. Therefore, detection of hypoglycemia must always be confirmed biochemically.³

Maternal risk factors for preterm delivery composes of maternal age⁴, parity⁵, social economy and psychosocial condition⁶, previous preterm delivery⁷, and life style⁸.

Neuregulin 1 plays an important role in the development of the lungs, heart, and brain. Neuregulin 1 assists synthesis of surfactant in the fetal lungs and functions as neuroprotector, and NRG 1 expression will effect according to gestational age and delivery risk factors.⁹ Researches regarding the role of NRG 1 in the neonatal population are still scarce, especially its association with blood glucose level in preterm infants.

The purpose of this study is to determine the association of neuregulin 1 level, maternal and neonatal risk factors, with blood glucose level in preterm infants.

MATERIAL AND METHODS

This was a cross sectional study, whereas 50 preterm infants with 32–36 weeks of gestational age through normal vaginal delivery and section caesarean were examined. Stillbirth and infants with severe congenital abnormalities were excluded. This study was conducted from June to August 2018 in four hospitals located in Medan, Indonesia.

Maternal characteristics such as maternal age, weight, gravidity and parity, and delivery methods were recorded as maternal risk factors. Neonatal characteristics such as gender, birth weight, gestational age, one-minute Apgar score, five-minute Apgar score were recorded as neonatal risk factors. Neuregulin 1 levels were obtained from the blood of umbilical cord during delivery. Blood glucose levels were obtained from venous blood sample and were checked serially from the time of delivery within the first hour of life until discharged from hospital or 72 hours of age. Blood glucose levels of 40 mg/dL or lower were considered as hypoglycemia. This study was approved by the Institutional Review Board of Universitas Sumatera Utara. Statistical data composed of univariate and bivariate were analyzed using SPSS version 22 (SPSS Inc., Chicago) with 95% confidence interval. P value <0.05 were considered statistically significant.

RESULT

Mean of maternal age were 30.9 years with mean of body weight were 69.3 kgs. A total of 96% gave birth through cesarean delivery where 58% having medical indications. There were 54% of premature infants had LBW (Table 1).

Table 1. Basic maternal and neonatal characteristic of subjects.

Characteristics	n = 50
Maternal age, years, mean + SD	30.9 + 5.23
>31 years	21 (42%)
<31 years	29 (58%)
Maternal weight, kg, mean + SD	69.3 + 10.87
>69 kg	25 (50%)
<69 kg	25 (50%)
Maternal gravidity, times, median (min-max)	2 (1 – 5)
>2	13 (26%)
1 – 2	37 (74%)
Maternal parity, times, median (min-max)	1 (0 – 2)
>1	8 (16%)
0 – 1	42 (84%)
Delivery, n (%)	2 (4%)
Vaginal delivery	48 (96%)
Sectio caesarean	

Indication of preterm labor, n (%)	29 (58%)
Medical indication	21 (42%)
Spontaneous	
Infant's gender, n (%)	25 (50%)
Male	25 (50%)
Female	
Birth weight, gram, mean + SD	2,503.5 + 542.21
<2500	27 (54%)
>2500	23 (46%)
Gestational age, weeks, n (%)	17 (34%)
32 – <35 weeks	33 (66%)
35 – <37 weeks	
Five-minute Apgar score, n (%)	0 (0%)
<3	1 (2%)
4-6	49 (98%)
>7	

Out of 50 preterm infants, there were 13 infants who developed hypoglycemia (26%). Regarding maternal risk factors, there was no association between maternal risk factors with hypoglycemia in the preterm infants. Regarding neonatal risk factors, preterm infants with gestational age of 32-<35 weeks and birth weight of ≤2500 gr were more likely to develop hypoglycemia (P=0.021 and P=0.010, respectively) (Table 2).

Neuregulin 1 levels in all the subjects had median value of 180,6 pg/mL. Twenty-five subjects (50%) had higher NRG 1 level (≥181 pg/mL), while other 25 subjects (50%) had lower NRG 1 level (<181 pg/mL) (Table 3). Preterm infants with hypoglycemia had lower NRG 1 levels compared to their counterparts (P=0.010) (Table 4).

Table 2. Association between maternal and neonatal risk factors with hypoglycemia in preterm infants

Variable	Hypoglycemia		Total n (%)	P	PR (95% CI)
Maternal age	Yes n (%)	No n (%)		0.314	1.91 (0.53-6.87)
>31 years	7 (33.3)	14(66.7)	21 (100)		
<31 years	6 (20.7)	23(79.3)	29 (100)		
Maternal weight				0.747	0.86 (0.34-2.19)
>69 kg	6 (24)	19 (76)	25 (100)		
<69 kg	7 (28)	18 (72)	25 (100)		
Maternal gravidity	2 (15.4)	11 (84.6)	13 (100)	0.469	0.52 (0.13-2.03)
>2	11 (29.7)	26 (70.3)	37 (100)		
Mode of delivery	13 (27.1)	35 (72.9)	48 (100)	0.392	-
Section caesaria	0 (0)	2 (100)	2 (100)		
Spontaneous					
Maternal parity	0 (0)	8 (100)	8 (100)	0.093	1.45 (1.18-1.77)
>1	13 (31)	29 (69)	42 (100)		
0 – 1					
Indication of preterm labor				0.340	1.63 (0.58 – 4.59)
Medical	9 (31)	20 (69)	29 (100)		
Spontaneous	4 (19)	17 (81)	21 (100)		

Gestational age	8 (47.1)	9 (52.9)	17 (100)	0.021*	3.11 (1.2-8.05)
32 – <35 weeks	5 (15.2)	28(84.8)	33 (100)		
35 – <37 weeks					
Infant's gender	6 (24)	19(76)	25 (100)	0.747	0.86 (0.34-2.19)
Male	7 (28)	18 (72)	25 (100)		
Female					
Birth weight <2,500 gr	11 (40.7%)	16 (59.3)	27 (100)	0.010*	4.69 (1.16-19)
>2,500 gr	2 (8.7%)	21 (91.3)	23 (100)		
5 minute Apgar score <7	0 (0)	1 (100)	1 (100)	1.000	1.36 (1.15-1.61)
>7	13 (26.5)	36 (73.5)	49 (100)		

P<0.05

Table 3. Neuregulin 1 levels in the cord blood

Variable	n = 50
NRG 1 levels, median (min-max), pg/mL	180,6 (121,1 – 6602,6)
High (>181)	25 (50%)
Low (<181)	25 (50%)

Table 4. Association of NRG 1 levels with hypoglycemia in preterm infants

Hypoglycemia	Mean NRG 1 levels	P
Yes	177.6	0.010
No	497.1	

Linear regression test showed that significant risk factor(s) associated with hypoglycemia in preterm infants was NRG 1 levels, whereas lower NRG 1 levels (<181 pg/mL) had higher risk to develop hypoglycemia (P= 0,035; OR= 4.86) (Table 5).

Table 5. Risk factors for hypoglycemia in preterm infants

Risk factors	P	OR (IK 95%)
Gestational age 32-<35 weeks	0.831	1.17 (0.269 - 5.132)
Birth weight ≤2500 gr	0.382	1.93 (0.441 – 8.470)
NRG 1 levels <181 pg/mL	0.035	4.86 (1.116 – 21.161)

DISCUSSION

Hypoglycemia is common in neonates. The lowest blood glucose level in 2 hours of life which is generally due to physiological rather than pathological factors.10,11,12 Previous studies reported prevalence of hypoglycemia varied in neonates, approximately 15.1-29.1%.13,14,15,16 The prevalence of hypoglycemia is significantly higher in preterm infants. Singh et al. showed the prevalence of hypoglycemia in preterm infants and term infants were 19.05% vs 14.42%.17

Neuregulin (NRG) is signaling protein, expresses in maturity process of the brain18, plays important roles in homeostasis and hemodynamics in cardiovascular system19, increases the proliferation of epithelial cells in the lungs20, and enhances the systemic glucose homeostasis21.

Maternal risk factors for preterm delivery composes of maternal age4, parity5, social economy and psychosocial condition6, previous preterm delivery7, and life style8.

This recent study found the prevalence of hypoglycemia in preterm infants was 26%. This prevalence difference is due to differences in the definition of hypoglycemia, inclusion criteria, sample size, and detection method of hypoglycemia.

There was no association between maternal risk factors with

hypoglycemia in the preterm infants. Regarding neonatal risk factors, birth weight and gestational age were associated with hypoglycemia. Preterm infants with birth weight of ≤ 2500 gr were significantly increased risk of 4.69 times experiencing hypoglycemia compared to birth weight > 2500 gr. Preterm infants with gestational age of 32– <35 weeks were had higher risk of 3.11 times experiencing hypoglycemia compared to preterm infants with gestational age of 35 – <37 weeks. This result was in line with previous studies.^{17,22} Neuregulin 1 levels had median of 180,6 pg/mL. Preterm infants who developed hypoglycemia had lower NRG 1 levels compared to their counterpart. Significant associated risk factors to hypoglycemia is NRG 1 levels, whereas low NRG 1 levels (<181 pg/mL) had higher risk to develop hypoglycemia. As far as our knowledge, this is the first study to determine the association. In the first week of life, premature and LBW infants are prone to hypoglycemia because their small reserves and immature metabolic pathways. After birth, the transplacental glucose supply is interrupted, while vital organs require continuous glucose supply to meet nutritional needs. Simultaneously, glycolytic hormones increase, partially suppressing insulin secretion. Premature infants become prone to hypoglycemia due to the limited glycogen and fat stores, lack of ability to generate glucose through the gluconeogenesis pathway, have a high metabolic demand due to relatively higher brain size, and have a poorly developed counter-regulatory mechanisms to prevent hypoglycemia.^{23,24,25} The American Academy of Pediatrics (AAP) recommends hypoglycemia screening in high-risk populations including premature infants.²⁶

The limitation of this study is that infant of diabetic mother was not analyzed as a risk factor for hypoglycemia in preterm infants and breastfeeding in the delivery room could not be anticipated even though the amount are expected to be almost negligible.

CONCLUSIONS

There was no association between maternal risk factors with hypoglycemia. Regarding neonatal risk factors, birth weight of ≤ 2500 gr and gestational age of 32– <35 weeks were associated with hypoglycemia. NRG 1 levels had median of 180,6 pg/mL. Preterm infants who developed hypoglycemia had lower NRG levels compared to their counterparts. Significant associated risk factors to hypoglycemia was NRG 1 levels, whereas low NRG 1 levels (<181 pg/mL) had higher risk to develop hypoglycemia.

Acknowledgement

The authors gratefully acknowledge that the present research is supported by Ministry of Research and Technology and Higher Education Republic of Indonesia. The support is under the research grant TALENTA USU of Year 2018 Contract Number 300/UNS.2.3.1/PPM/KP-TALENTA USU/2018. We also thank H Adam Malik Hospital Medan, Stella Maris Hospital Medan, Sarah Hospital Medan and Bunda Thamrin Hospital Medan.

REFERENCES

- Howson C, Kinye M., Lawn J. Born too soon: the global action report on preterm birth. WHO, Geneva. 2012; 19–26.
- Zanardo V, Cagda S, Golin R, Trevisanuto D, Marzari F, Rizzo L. Risk factors of hypoglycemia in premature infants. *Fetal Diagn Ther*. 1999;14:63–67.
- Dhananjaya, C., Kiran, B. Clinical profile of hypoglycemia in newborn babies in a rural hospital setting. *Int J Biol Med Res*. 2011;2:1110–1114.
- Elyahu S, Weiner E, Nachum Z, Shalev E. Epidemiologic risk factors for preterm delivery. *IMAJ*. 2002;4:1115–1117.
- Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: A large cohort study. *PLoS ONE*. 2018;13(1):e0191002.
- Motquin JM. Socio-economic and psychosocial factors in the management and prevention of preterm labour. *BJOG*. 2003;110:56–60.
- Macones G. Prematurity: causes and prevention. In: Taeusch, HW, Ballard, RA, Gleason, CA, editors. *Avery's disease of the newborn*, ed 8. Pennsylvania: Elsevier Saunders, 2005.p.139–145.
- Goldenberg RL, Culhane JF, Lams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371:75–84.
- Pleickhardt EP, Celandine A, Davis, J, Chen M, Schurmann P, Dork, T. Neuregulin 1 high-producer genotype is associated with a decreased risk of admission to the neonatal intensive care unit. *Early Human Development*. 2010;86: 299–304.
- Sperling M. Hypoglycemia. In: Kliegman R M, Behrman R E, Jensen H B and Stanton B F, editors. *Nelson textbook of pediatrics*. Philadelphia: Elsevier Inc, 2012.p.517–531.
- Mitanchez D. Glucose regulation in preterm newborn infants. *Horm Res*. 2007;68:265–271.
- Aggarwal R., Sankar M, Agarwal R., Deorari A, Paul V. Hypoglycemia in the newborn. *J*

- Pediatr*. 2010;109:114–126.
- Lodhi M, Shah N, Shabir G. Risk factors associated with neonatal hypoglycemia. *Proc Med J*. 2006;16:687–690.
- Dashti N, Einollahi N, Abbasi S. Neonatal hypoglycemia: prevalence and clinical manifestations in Tehran Children's Hospital. *Park J Med Sci*. 2007;23:340–343.
- Osiet F, Berkley J, Ross A, Sanderson F, Mohammed S, Newton C. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: prevalence and outcome. *Arch Dis Child*. 2003;88:621–625.
- Dalgic N, Ergenekon E, Soysal S, Koc E, Atalay Y, Gucuyener K. Transient neonatal hypoglycemia – long term effects on neurodevelopmental outcome. *J Pediatr Endocrinol Metab*. 2002;15:19–24.
- Singh Y, Devi T, Gangte D, Devi T, Singh N, Singh M. Hypoglycemia in newborn in Manipur. *J Med Soc*. 2014;28:108–111.
- Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nature Reviews Neuroscience*. 2008;9: 437–452.
- Lemmens L, Doggen K, De Keulenaer GW. Role of neuregulin 1/ErbB signaling in cardiovascular physiology and disease: implications for therapy of heart failure. *Circulation*. 2007;116:954–960.
- Patel NV, Acarregui MJ, Snyder JM, Klein JM, Sliwowski MX. Neuregulin 1 and human epidermal growth factor receptors 2 and 3 play a role in human lung development in vitro. *Am J Respir Cell Mol Biol*. 2000;22: 432–440.
- Canto C, Pich S, Paz JC, Sanches R, Martinez V, Orpinell M, et al. Neuregulin increase mitochondrial oxidative capacity and insulin sensitivity in skeletal muscle cells. *Diabetes*. 2007;56:2185–2193.
- Rasmussen A, Wehberg S, Fenger-Groen J, Christesen H. Retrospective evaluation of a National guideline to prevent neonatal hypoglycemia. *Pediatr Neonatol*. 2007;58:398–405.
- Ramzan M, Razzaq A, Kiyani A. Hypoglycemia in small for gestational age neonates based on gestational age, gender, birth weight, and mode of delivery. *Pak Armed Forces Med J*. 2017;67:397–400.
- Bromiker R, Perry A, Kasirer Y, Einav S, Klinger G, Levy-Khademi F. Early neonatal hypoglycemia: incidence of and risk factors. *J Matern Fetal Neonatal Med*. 2017;26:1–7.
- Sharma A, Davis A, Shekhawat P. Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, Management, and long term outcomes. *Transl Pediatr*. 2017;6:335–348.
- Adamkin D. Clinical Report-Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127:575–579.