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Risk Factors and Outcomes of Hyperglycemia in Low Birth Weight Infants: A Prospective Observational Study

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ABSTRACT

Background: Low birth weight (LBW) babies frequently have hyperglycemia, which is linked to greater mortality as well as morbidity. The threshold intervention and management protocols are controversial.

Objectives: To define the incidence of neonatal hyperglycemia, associated risk factors, and the outcome in LBW infants in tertiary Neonatal Intensive Care Units in Ain Shams University, Cairo, Egypt.

Patients and Methods: In a prospective observational trial, 125 low birth weight neonates were included in this study. Blood glucose concentration was monitored daily in all infants for 7 days. Insulin therapy was initiated if hyperglycemia >200 mg/dL despite reductions in glucose infusion rate. Outcomes were reported till 28 days of life.

Results: Twenty-four percent of the cohort developed hyperglycemia. Mortality and intraventricular haemorrhage (IVH) were significant outcomes and higher in the hyperglycemia group compared to euglycemia group. This could be related to the higher glucose levels and not to the duration of hyperglycemia. Twenty-three infant (76.7%) among the hyperglycemia group responded to decreasing glucose infusion rate (GIR) while 7 infants (23.3%) needed insulin; 3 (42.9%) improved, 4 (57.1%) had hypoglycemia attacks and died.

Conclusions: Among low birth weight infants' hyperglycemia was associated with morbidity and death. Using insulin as a line of treatment for hyperglycemia may be associated with hypoglycemic attacks and mortality.

Keywords: Insulin, Low birth weight babies, Hyperglycemia.

INTRODUCTION

During the first week of life, due to interrupted placental glucose transfer and disturbed glucose homeostasis most preterm neonates need glucose infusion to maintain the glucose level. Hyperglycemia eventually develops as a result of improper proinsulin processing by β-islet cells, partial insulin resistance, and a lack of inhibition of glucose synthesis during parenteral glucose infusion[(1)].

Although chronic neonatal hyperglycemia is linked to considerable morbidity and mortality, it may be a normal reaction to stress. It has been classified according on the absolute blood glucose level, the length of exposure, and whether or not glycosuria was present[(2)].

Depending on how the threshold is defined, the prevalence of hyperglycemia in preterm infants ranges from 15% to 30% [(3)]. It has an opposite relationship to birth weight[(4)].

In babies born very prematurely with very low birth weights, hyperglycemia can increase mortality, cause intraventricular haemorrhage (IVH), retinopathy of prematurity, necrotizing enterocolitis (NEC), increase oxidative stress, cause sepsis, prolong hospital stays, and impair physical growth until 2 years corrected age[(5-8)].

Recent research has shown that continuous glucose monitoring (CGM) can aid with glucose control and lower the risk of hypoglycemia in preterm infants[(2)].

The aim of this work is to define the incidence of neonatal hyperglycemia, associated risk factors and the outcomes for low birth weight (LBW) babies in Tertiary Neonatal Intensive Critical Care Units, Ain Shams University, Cairo, Egypt.

PATIENTS AND METHODS

The study included 125 LBW infants weighing less than 2500 grams at birth consecutively admitted to the NICU. All of the infants who were included underwent a full clinical examination, comprehensive history taking, and standard neonatal care. Prenatal trans-abdominal ultrasound and the modified Ballard scoring method[(9)] were used to confirm the gestational age, which was determined from the date of the most recent menstrual cycle.

Exclusion criteria: Infant of diabetic mothers, neonates with endocrinal diseases, congenital anomalies, or suspected chromosomal aberrations were excluded from the study. Hyperglycemia outcomes were reported till 28 days of life.

Blood glucose concentration was monitored for 7 days using the Bionime rightest blood glucose monitoring system GM300.

Blood glucose concentration was monitored daily in all infants receiving intravenous glucose infusions. Monitoring every 3-6 hours for newborns with stress, septicemia, or cases of extremely low birth weight (ELBW). The blood glucose level was measured within 30 minutes to 1 hour of the start of the insulin infusion and whenever the rate of glucose or insulin infusion varied. After becoming steady, glucose levels was checked every hour for the next 3-6 hours.

Hyperglycemia was defined according to blood glucose; mild (151 mg/dL to 180 mg/dL), moderate (181 mg/dL to 210 mg/dL) or severe (>210 mg/dL)[(10)].

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Management protocol of hyperglycemia:

Initiated at values above 180 mg/dl. The first step was to decrease the glucose infusion rate (GIR) by adjusting the concentration and/or the rate of glucose infusion. Insulin therapy was initiated if hyperglycemia >200 mg/dL despite reductions in GIR. Continuous insulin infusion; 0.01 to 0.2 units/kg/hour with blood glucose monitoring every 30 minutes until stable. If the blood glucose level stayed above 180 mg/dL, titrate in 0.01 unit/kg/hour increments. If hypoglycemia occurs, stop the insulin infusion and provide one IV bolus of 10% dextrose at 2 ml/kg while keeping an eye out for relapses of hyperglycemia. Outcomes were reported till 28 days of life or discharge form NICU whichever comes first.

Ethical considerations:

Parent(s) of newborns gave their informed consents before participating in this prospective observational study, which was conducted at the NICU, Ain Shams University. The Pediatric Department's Council, part of the Faculty of Medicine, Ain Shams University, gave the study its ethical approval. This work has carried-out in accordance with The Code of Ethics of the World Medical Association [(11)], Declaration of Helsinki for studies involving humans.

Statistical analysis:

Data were gathered, coded, reviewed, and put into IBM SPSS version 20 of the Statistical Package for Social Science (SPSS). For the quantitative data having a parametric distribution, the data were provided as mean, standard deviations, and ranges. For the non-parametric data, the median was reported with interquartile ranges (IQR). When comparing two groups using qualitative data, the Chi-square test was applied, and the Fisher exact test was applied in its place when the predicted count in any cell was less than 5. Independent t-test was used to compare two independent groups with quantitative data and parametric distribution, whereas Mann-Whitney test was used to compare two independent groups with non-parametric data. F-test was used to compare >2 independent groups with quantitative data. The risk ratio (RR) and 95% confidence interval for the odds ratio were calculated through the use of logistic regression analysis. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. In all analyses, a P-value of 0.05 or below was regarded as the threshold for significance.

RESULTS

One hundred and twenty-five infants weighing less than 2.500 grams at birth were enrolled in the study, 30 (24%) comprised the hyperglycemia group and 95 (76%) comprised the euglycemia group. Mild hyperglycemia was found in 12 infants (40%), while moderate hyperglycemia was found in 3 (10%), while severe hyperglycemia was present in 15 (50%) of hyperglycemia group. Mean duration of hyperglycemia was 36.39 ± 18.46 hours, with a maximum glucose level of 301.20 ± 105.11 mg/dL.

Table (1): Demographic and clinical data of the studied neonates (n=125).

Variables		Euglycemia n=95	Hyperglycemia n=30	χ^2-value* t-value** Mann-Whitney¥	
		No. (%)	No. (%)	Test	p-value
Sex	Female	56 (58.9)	17 (56.7)	0.048*	0.825
	Male	39 (41.1)	13 (43.3)		
	M : F ratio	1 : 1.4	1 : 1.3		
Caesarean section delivery		76 (80.0)	26 (86.7)	0.674*	0.411
Parity	Primigravida	27 (28.4)	12 (40.0)	1.603*	0.448
	1 – 3	56 (58.9)	14 (46.7)		
	> 3	12 (12.6)	4 (13.3)		
Birth weight (kgs, Mean ±SD)		1.61 ± 0.40	1.35 ± 0.36	3.355**	0.001#
Apgar score 1 min (Median, IQR)		7 (5 – 7)	6 (3 – 6)	3.961¥	0.000#
Apgar score 5min (Median, IQR)		8 (7 – 9)	7 (7 – 8)	3.515¥	0.001#
Gestational age (week, Mean ±SD)		33.72 ± 2.50	31.59 ± 2.15	4.542**	0.000#
Maturity	Preterm	78 (82.1)	25 (83.3)	0.744*	0.689
	Late preterm	7 (7.4)	1 (3.3)		
	Full term	10 (10.5)	4 (13.3)		
Birth weight	Low	41 (43.2)	6 (20.0)	22.29*	0.00001#
	Very low	54 (56.8)	18 (60.0)		
	Extremely low	0 (0.0)	6 (20.0)		
Multiple pregnancy		22 (23.2)	10 (33.3)	1.239*	0.265

*χ^2, **t-test, ¥Mann-Whitney, #Significant

Demographic and clinical data for all included neonates were shown in table (**1**); Birth weight, APGAR at 1&5 minutes, and gestational age were lower in the hyperglycemia compared to the euglycemia group with statistically significant differences. Mode of delivery, parity, multiple pregnancy and maturity were comparable in the euglycemia and hyperglycemia groups.

Maternal and neonatal characteristics of all included neonates were shown in table (**2**). In hyperglycemia group, pre-eclampsia (total), premature rupture of membrane (PROM), chorio-amnionitis, and antepartum hemorrhage were significantly higher and risk factors of hyperglycemia in LBW neonates (RR=1.23, 2.78, 3.69, 3.66; respectively). While other maternal diseases showed insignificant difference between the study groups. While stable grower neonates, neonatal respiratory distress, sepsis, jaundice, and hypoxia showed statistically insignificant difference between the study groups and were insignificant risk factors.

There were no differences in the rates of glucose infusion between the study groups during the observation period from day 2 to day 7 of life (table**3**).

Outcomes are shown in table (**4**), NEC showed insignificant difference while mortality and IVH were significantly higher in the hyperglycemia group compared to euglycemia group. Moreover, NEC, mortality, and IVH could be related to the higher glucose levels and not to the duration of hyperglycemia (table**5**).

Table (2): Maternal and neonatal characteristics of the two studied groups (n=125).

Variables		Euglycemia n= 95	Hyperglycemia n= 30	Chi-square test		RR	95% CI
		No. (%)	No. (%)	X^2	P-value		
Oligohydramnios		4 (4.2)	1 (3.3)	0.045	0.83	0.827	0.13 - 4.91
Maternal pre-eclampsia	Mild PET	9 (9.5)	0 (0.0)	3.06	0.08	0.00	0.0 - 0.0
	SPET	21 (22.1)	4 (13.3)	1.09	0.295	0.615	0.23 - 1.6
	HTN	2 (2.1)	1 (3.3)	0.14	0.701	1.4	0. 27 - 7.16
	HELLP	2 (2.1)	0 (0.0)	0.64	0.423	0.00	0.0 - 0.0
	Total	34 (35.8)	5 (16.7)	3.88	0.048*	1.23	1.19 - 1.46
Maternal infection	PROM	18 (18.9)	15 (50.0)	11.31	0.0007*	2.78	1.53 – 5.05
	Chorioamnionitis	4 (4.2)	9 (30.0)	16.27	0.0000*	3.69	2.17 - 6.26
	Total	22 (23.2)	24 (80.0)	31.67	0.000*	13.27	4.81 – 36.57
Maternal haemorrhage	Acc. Hemorrhage	1 (1.1)	3 (10.0)	5.89	0.01*	3.66	1.74 - 6.47
	PP	15 (15.8)	2 (6.7)	1.61	0.203	1.19	0.96 - 1.46
	Aphge	10 (10.5)	3 (10.0)	0.006	0.934	1.01	0.73 -13.38
	Total	26 (27.4)	8 (26.7)	0.005	0.939	1.008	0.81 – 1.25
Maternal diseases	SLE	1 (1.1)	0 (0.0)	0.318	0.572	0.00	0.0 - 0.0
	Asthmatic	1 (1.1)	1 (3.3)	0.75	0.385	2.12	0.51 - 8.79
	Fe def. anemia	1 (1.1)	0 (0.0)	0.318	0.572	0.00	0.0 - 0.0
	ITP	2 (2.1)	0 (0.0)	0.64	0.423	0.00	0.0 - 0.0
	Total	5 (5.3)	1 (3.3)	0.185	0.666	0.68	0.11 - 3.2
Stable grower neonate		16 (16.8)	1 (3.3)	3.54	0.059	0.21	0.03 - 1.5
Neonatal Respiratory Distress	Total	42 (44.2)	15 (50.0)	0.308	0.578	1.19	0.63 - 2.22
	RDS	34 (35.8)	13 (43.3)	0.553	0.457	1.26	0.67 – 2.37
	MAS	5 (5.3)	2 (6.7)	0.085	0.771	1.20	0.35 - 4.05
	TTN	3 (3.2)	0 (0.00)	0.97	0.324	0.00	0.0 - 0.0
Neonatal Sepsis	Total	13 (13.7)	5 (16.7)	0.164	0.685	1.18	0.52 - 2.69
	EONS	6 (6.3)	3 (10.0)	0.46	0.496	1.43	0.53 – 3.82
	Pneumonia	7 (7.4)	2 (6.7)	0.016	0.896	0.92	0.26 - 3.25
Hypoxic ischemic encephalopathy		1 (1.1)	0 (0.00)	0.318	0.572	0.00	0.0 - 0.0
Neonatal jaundice		6 (6.3)	3 (10.0)	0.46	0.496	1.43	0.53 – 3.82
RDS + sepsis		17 (17.9)	6 (20)	0.067	0.795	1.1	0.51 – 2.39

*****Significant, **CI:** Confidence interval, **RR:** Risk ratio, **SPET:** Severe pre-eclampsia, **HTN:** Hypertension, **PROM:** Premature rupture of membranes, **PP:** Placenta Previa, **Aphge:** Antepartum haemorrhage, **SLE:** Systemic lupus erythromatosis, **ITP:** Idiopathic thrombocytopenic purpura, **RDS:** Respiratory distress syndrome.

Table (3): Glucose infusion rates (GIR) during the study period (n=125).

GIR gm/kg/min	Euglycemia n=95	Hyperglycemia n=30	t-test	
	Mean ± SD	Mean ± SD	t	P-value
Day 1	4.13 ± 0.52	3.82 ± 0.66	2.325	0.02*
Day 2	4.47 ± 1.05	4.37 ± 0.77	0.565	0.575
Day 3	4.92 ± 1.21	5.2 ± 1.12	-1.17	0.247
Day 4	5.08 ± 1.16	5.28 ± 1.19	-0.807	0.427
Day 5	4.85 ± 1.20	5.28 ± 1.31	-1.599	0.12
Day 6	4.93 ± 1.13	5.23 ± 1.21	-1.202	0.234
Day 7	4.66 ± 1.11	5.06 ± 1.13	-1.697	0.09

*****Significant

Table (4): Outcomes of the study groups (n=125).

Variables	Euglycemia n=95	Hyperglycemia n=30	Chi-square test	
	No. (%)	No. (%)	X^2	P-value
Mortality	2 (2.1)	5 (16.7)	9.144	0.002*
Necrotizing enterocolitis (NEC)	4 (4.2)	3 (10.0)	1.445	0.229
Intraventricular haemorrhage (IVH)	2 (2.1)	6 (20.0)	12.187	0.0004*

*****Significant

Table (5): Outcomes versus maximum glucose level & duration of hyperglycemia (n=30).

Outcome	Maximum glucose level (mg/dl)	Duration of hyperglycemia (hours)
Necrotizing enterocolitis (Mean ±SD)	286.00 ± 61.18	32.00 ± 7.73
Intraventricular haemorrhage (Mean ±SD)	324.33 ± 17.21	31.14 ± 7.24
Mortality (Mean ±SD)	417.60 ± 60.82	28.80 ± 6.73
F-test	53.22	1.567
P-value	0.000*	0.214

*****Significant

Table (**6**) shows the medication and support received during the study period. Double and triple antibiotics use, inotropic support blood products, total parenteral nutrition, IVIG, and the need for conventional ventilation group were higher in the hyperglycemia group compared to the euglycemia group. However, use of triple antibiotics is more significant than the double.

Table (6): Medications and support received during the observation period of the two studied groups (n=125).

Variables	Euglycemia n=95	Hyperglycemia n=30	Chi-square test	
	No. (%)	No. (%)	X^2	P-value
Single antibiotic	8 (8.4)	0 (0.0)	2.699	0.1004
Double antibiotic	39 (41.1)	6 (20.0)	4.386	0.036*
Triple antibiotic	48 (50.5)	23 (76.7)	6.349	0.011*
Inotropic support	1 (1.1)	15 (50.0)	48.94	0.000*
Blood products	7 (7.4)	15 (50.0)	28.573	0.000001*
TPN	55 (57.9)	25 (83.3)	6.403	0.011*
IVIG	4 (4.2)	8 (26.7)	13.248	0.0002*
Magnesium sulphate	3 (3.2)	0 (0.0)	0.97	0.324
Surfactant	0 (0.0)	1 (3.3)	3.192	0.073
Anticonvulsants	2 (2.1)	2 (6.7)	1.531	0.215
Nasal CPAP	19 (20.0)	6 (20.0)	0.0	1.0
Nasopharyngeal CPAP	9 (9.5)	1 (3.3)	1.168	0.279
Conventional mechanical ventilation	22 (23.2)	19 (63.3)	16.696	0.00004*
High frequency ventilation	5 (5.3)	1 (3.3)	0.185	0.666

*****significant, **TPN:** Total parenteral nutrition, **IVIG:** Intravenous immunoglobulins, **CPAP:** Continuous positive airway pressure

Figure (**1**) shows flow diagram for management of hyperglycemia through the study period; 23 (76.7%) among the hyperglycemia group responded to decreasing GIR while 7 infants (23.3%) needed insulin; 3/7 (42.9%) improved, 4/7 (57.1%) had hypoglycemia attacks and died.

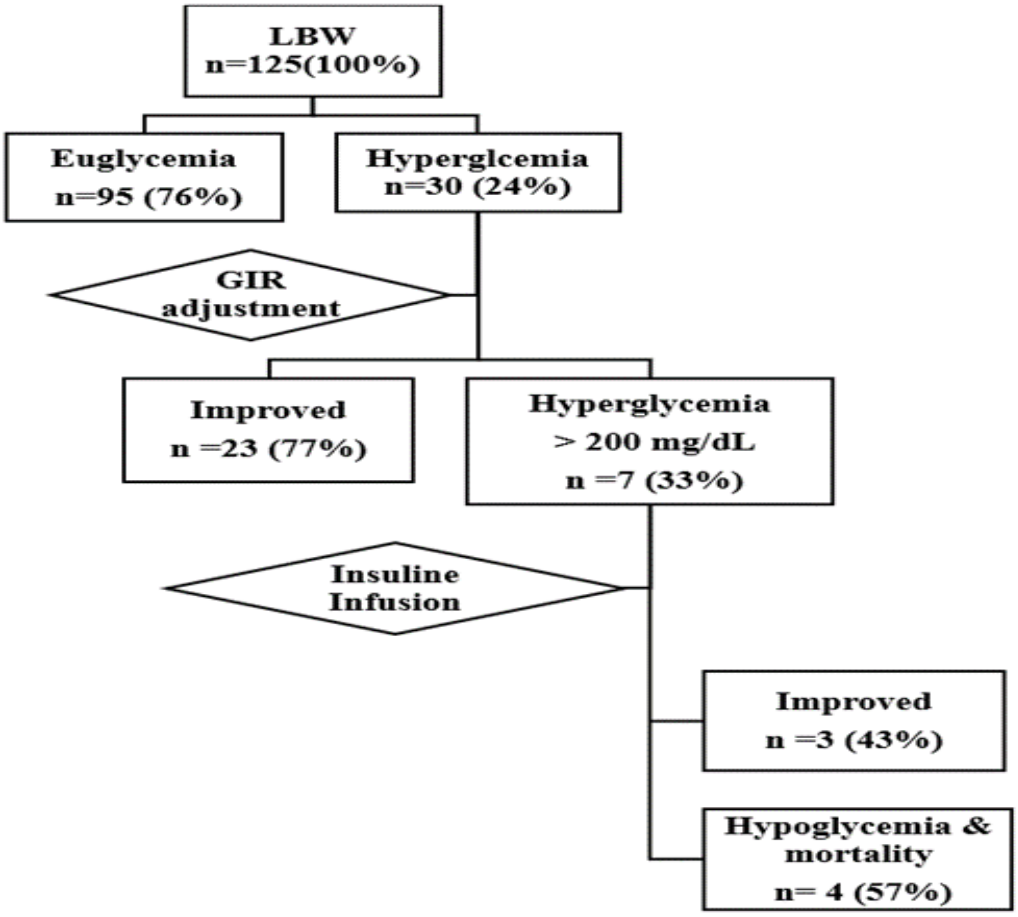

Figure (1): Flow diagram for management of hyperglycemia through the study period.

DISCUSSION

In the present study hyperglycemia occurred in 24% of LBW cohort. Incidence of hyperglycemia in literatures ranges widely between 88% and 32%[6,12-14]. These differences may be due to the lack of consensus on the definition of hyperglycemia, which is commonly defined as blood glucose ≥180 mg/dl[15]. Yet, glucose ≥145 mg/dl is must be prevented, as advised by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition[16] since it is linked to greater morbidity and mortality.

In the current study there is no sex difference in the incidence of hyperglycemia. **Dickson *et al.*[17]** found the same. However, girls had higher insulin secretion, at similar blood glucose and plasma insulin concentrations than boys, this may reflect a difference in insulin sensitivity in hyperglycemic preterm girls.

According to the present study, euglycemic newborns were younger and have a higher birth weight than hyperglycemic neonates. **Decaro and Vain[6]** attributed this to decreased hepatic insulin sensitivity and inadequate processing of proinsulin by immature pancreatic cells, which caused glucose instabilities seen even in stable enterally-fed, well-developing preterm neonates[18].

In this study, significant risk factors among the hyperglycemia were maternal pre-eclampsia (total) (RR=1.32, 95% CI:1.19-1.46), chorioamnionitis (RR=3.69, 95% CI:2.17-6.26), and accidental hemorrhage (RR=3.36, 95% CI:1.74-6.47) compared to the euglycemia group. Placental insufficiency and chorioamnionitis had strong association with increased risk of severe hyperglycemia[13].

The association between maternal pre-eclampsia and neonatal hyperglycemia may be explained by the fact that hypertensive mother has significant association with LBW and prematurity, which are associated with hyperglycemia. In contrast to these results, **Blanco *et al.*[12]** demonstrated that chorioamnionitis in the mother decreased the likelihood of hyperglycemia in the infant. Contradictory results on the protective effects of chorioamnionitis with hyperglycemia were discovered; the reason for this association requires more research.

Regarding neonatal diagnosis, in the current study, stable growing infants showed more euglycemic

control. Respiratory distress (RD) and/or sepsis were comparable in both euglycemic and hyperglycemic infants. However, receiving double and triple antibiotics, inotropic support and need for respiratory support especially mechanical ventilation were higher in hyperglycemia group compared to the euglycemia group.

In a newborn with previously normal blood glucose levels, hyperglycemia may be the first symptom of sepsis. It is significantly associated with RD and its consequences. Additionally, in VLBW, hyperglycemia can worsen sepsis[8].

Using Dopamine as inotropic support may affect blood glucose by reducing insulin secretion and increasing insulin unresponsiveness[19].

Selected amino acid can modulating insulin resistance, administering an extra gram of protein reduces hyperglycemia and higher plasma amino acid can counteract the catabolic state associated with hyperglycemia. Moreover, intralipid may act through insulin sensitivity disturbance and increasing the substrate for glucogenesis[19-21]. In this study, total parenteral nutrition (TPN) was used more in the hyperglycemia group compared to euglycemia group.

Current results show no difference in the rate of glucose infusion among euglycemia and hyperglycemia groups. In the current investigation, GIR was less than 6 mg/kg/minute, which may be related to the clinical finding of high glucose levels that led to a clinical decision to limit the dextrose infusion rate[13].

Regarding the outcomes, current results demonstrate higher mortality and IVH in the hyperglycemia group compared to euglycemia group. Moreover, the NEC, mortality, IVH could be related to the maximum glucose levels and not to the duration of hyperglycemia. **Auerbach *et al.*[22]** claimed that severe IVH was highly correlated with longer duration of hyperglycemia in the first 96 hours of life, and that this relationship was mostly based on length rather than amplitude of hyperglycemia. **Van der Lugt *et al.*[23]** showed correlation between mean and maximal glucose levels on days 3 and 4 of hyperglycemia episodes, but not with the length of hyperglycemia, and infant death.

As per management, most of the hyperglycemia group responded to lowering GIR while only quarter needed insulin; 42.9% of neonates who received insulin improved, while 57.1% had hypoglycemia attacks and eventually died.

In the ninetieth, **Meetze *et al.*[24]** proved the effectiveness of continuous insulin infusion in glucose control. Babies given insulin experienced higher glucose intake, more weight gain, reduced sepsis, and increased endogenous insulin production. Later, **Beardsall *et al.*[25]** revealed that although early elective insulin therapy reduces hyperglycemia, it dramatically raises the risk of hypoglycemia and mortality by the first 28 days of life, raising doubts about its effectiveness in the prevention and treatment of hyperglycemia in premature infants. More recently, the long-term effects of early hyperglycemia in VLBW infants did not yield reliable advice for how to address the condition[26].

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Limitation and Strength Points of the Study:

Limitations of the study include it's a one, single center study and we didn't measure glucose in urine to detect neonates with glycosuria. Simultaneously, strength of the study include it's a prospective design, which enabled us to define the incidence and determine accurately the risk factors.

CONCLUSIONS

Low birth weight infants' hyperglycemia is associated with morbidity and death. Using insulin as a line of treatment for hyperglycemia may be associated with hypoglycemic attacks and mortality.

We recommend conduct more studies on large number of neonates in different NICUs in different geographical areas to define the true incidence, risk factors, and management of this problem

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REFERENCES

1. **Mitanchez D (2007):** Glucose regulation in preterm newborn infants. Horm Res., 68(6):265-71.
2. **Beardsall K (2021):** Hyperglycaemia in the Newborn Infant. Physiology Verses Pathology. Front Pediatr., 9:641306. doi: 10.3389/fped.2021.641306
3. **Ramel S, Rao R (2020):** Hyperglycemia in Extremely Preterm Infants. Neo Reviews, 21(2): 89-97. doi: 10.1542/neo.21-2-e89.
4. **Le Compte A, Lynn A, Lin J *et al.* (2012):** Pilot study of a model-based approach to blood glucose control in very-low-birthweight neonates. BMC Pediatr., 12:117. doi: 10.1186/1471-2431-12-117.
5. **Parappil H, Gaffari M, Paramban R *et al.* (2022):** Management of hyperglycemia in the neonatal unit: A practical approach to diagnosis and management. J Clin Neonatol., 11:38-44.

6. **Decaro M, Vain N (2011):** Hyperglycaemia in preterm neonates: what to know, what to do. Early Hum Dev., 87 (1): 19-22.
7. **Alexandrou G, Karlén J, Tessma M *et al.* (2010):** Early Hyperglycemia Is a Risk Factor for Death and White Matter Reduction in Preterm Infants. Pediatrics, 125: 584–591.
8. **Ramel S, Long J, Gray H *et al.* (2013):** Neonatal hyperglycemia and diminished long-term growth in very low birth weight preterm infants. J Perinatol., 33(11):882-6.
9. **Ballard J, Khoury J, Wedig K *et al.* (1991):** New Ballard Score, expanded to include extremely premature infants. J Pediatr., 119(3):417-23.
10. **Kaempf J, Kaempf A, Wu Y *et al.* (2011):** Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity. J Perinatol., 31(4):251-7.
11. **World Medical Association (2013):** Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. JAMA., 310 (20): 2191-2194.
12. **Blanco C, Baillargeon J, Morrison R *et al.* (2006):** Hyperglycemia in extremely low birth weight infants in a predominantly Hispanic population and related morbidities. J Perinat., 26:737– 41.
13. **Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart A *et al.* (2007):** A randomised controlled trial of early insulin therapy in very low birth weight infants, ‘‘NIRTURE’’ (neonatal insulin replacement therapy in Europe). BMC Pediatr., 7: 29. doi: 10.1186/1471-2431-7-29
14. **Kao L, Morris B, Lally K *et al.* (2006):** Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol., 26(12):730-6.
15. **Alsweiler J, Kuschel C, Bloomfield F (2007):** Survey of the management of neonatal hyperglycaemia in Australasia. J Paediatr Child Health, 43:632–5.
16. **Mesotten D, Joosten K, van Kempen A *et al.* (2018):** ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Carbohydrates. Clin Nutr., 37(6 Pt B):2337–43.
17. **Dickson J, Chase J, Pretty C *et al.* (2015):** Hyperglycaemic Preterm Babies Have Sex Differences in Insulin Secretion. Neonatology, 108(2):93-98.
18. **Mola-Schenzle E, Staffler A, Klemme M *et al.* (2015):** Clinically stable very low birthweight infants are at risk for recurrent tissue glucose fluctuations even after fully established enteral nutrition. Arch Dis Child Fetal Neonatal Ed., 100(2): 126-31.
19. **Sabzehei M, Afjeh S, Shakiba M *et al.* (2014):** Hyperglycemia in VLBW Infants; Incidence, Risk Factors and Outcome. Arch Iran Med., 17(6): 429 – 34.
20. **Burattini I, Bellagamba M, Spagnoli C *et al.* (2013):** Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: a randomized clinical trial. J Pediatr., 163(5):1278-82.
21. **Rozance P, Hay W (2010):** Describing hypoglycemia--definition or operational threshold? Early Hum Dev., 86(5):275-80.
22. **Auerbach A, Friedman S, Arad I *et al.* (2013):** Long duration of hyperglycemia in the first 96 hours of life is associated with severe intraventricular hemorrhage in preterm infants. J Pediatr., 163(2):388-93.
23. **Van der Lugt N, Smits-Wintjens V, van Zwieten P *et al.* (2010):** Short- and long-term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. BMC Pediatr., 10: 1-7.
24. **Meetze W, Bowsher R, Compton J *et al.* (1998):** Hyperglycemia in extremely- low-birth-weight infants. Biol Neonate, 74: 214-21.
25. **Beardsall K, Ogilvy-Stuart A, Frystyk J *et al.* (2007):** Early Elective Insulin Therapy Can Reduce Hyperglycemia and Increase Insulin-Like Growth Factor-I Levels in Very Low Birth Weight Infants. J Pediatr., 151: 611-7.
26. **Paulsen M, Brown S, Satrom K *et al.* (2021):** Long-Term Outcomes after Early Neonatal Hyperglycemia in VLBW Infants: A Systematic Review. Neonatology, 118(5):509-521.
27. **Sinclair J, Bottino M, Cowett R (2011):** Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev., 10: CD007615. doi: 10.1002/14651858.CD007615.
28. **Heald A, Abdel-Latif M, Kent A (2012):** Insulin infusion for hyperglycaemia in very preterm infants appears safe with no effect on morbidity, mortality and long-term neurodevelopmental outcome. J Matern Fetal Neonatal Med., 25(11):2415-8.
29. **Picard M, Juster R, McEwen B (2014):** Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. Nat Rev Endocrinol., 10: 303–310.