Original Article

Hyperglycemia in VLBW Infants; Incidence, Risk Factors, and Outcome

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Abstract

Background: Neonatal hyperglycemia, which is relatively common in very low birth weight (VLBW) infants, is associated with increased risk of morbidity and mortality.

Objective: To study the incidence of neonatal hyperglycemia, associated risk factors and the outcome of it in VLBW infants hospitalized in a level III NICU in Tehran.

Methods: All VLBW newborns admitted to the NICU of Mahdieh Hospital from April 2009 to March 2011 were considered eligible for this retrospective study. All relevant prenatal and perinatal data, as well as details of the hospital stay until discharge or death, were extracted from the case notes and analyzed.

Results: Hyperglycemia (blood suger above 150mg/dL) was observed in 179 (31.7%) of the 564 VLBW infants included in the study; 48 infants (26.8%), had received insulin. Risk factors included: low gestational age, (OR = 4.07, 95% CI = 2.09–7.93, *P* < 0.001), extremely low birth weight (ELBW) , (OR = 5.97, 95% CI = 3.77–9.44, *P* < 0.001), dopamine administration (OR = 2.19, 95% CI = 1.32–3.65, *P* = 0.003), intralipid (OR = 1.52, 95% CI = 1.04–2.22, *P* = 0.03), Low APGAR score at 5 minutes (OR = 4.44, 95% CI = 2.48–7.94, *P* < 0.001), RDS and its complications (OR = 4.20, 95% CI = 2.55–6.93, *P* < 0.001), were independently associated with hyperglycemia.

Other findings with hyperglycemia were: high incidence of IVH >grade II (OR = 2.88, 95% CI = 1.28–6.49, *P* = 0.01), hospital stay more than 28 days in survivors,(OR = 3.56, 95% CI = 2.02–6.25, *P* < 0.001), mortality (OR = 4.42, 95% CI = 3.00–6.52, *P* < 0.001) and more retinopathy of prematurity (ROP ≥ stage II) in survivors (OR = 2.05, 95% CI = 1.11–3.78, *P* = 0.02).

Conclusion: Neonatal hyperglycemia developed in approximately one-third of our VLBW neonates. Relative prevalence and associated findings underscore the need for preventive measures and prompt management.

Keywords: Mortality, neonatal hyperglycemia, risk factors, very low birth weight infants

Cite this article as: Sabzehei MK, Afjeh SA, Shakiba M, Alizadeh P, Shamshiri AR, Esmaili F. Hyperglycemia in VLBW Infants; Incidence, Risk Factors and Outcome. *Arch Iran Med*. 2014; **17(6):** 429 – 434.

Introduction

Although hyperglycemia is common in very low birth weight (VLBW) infants, particularly in extremely low birthweight (ELBW) neonates, still no consensus has been reached on a specific blood sugar level that would define hyperglycemia in neonates. In 1976, Cornblath found that 2% of neonates had a blood sugar (BS) of > 125 mg/dL or a plasma sugar of >150 mg/dL and proposed that these levels should be used for hyperglycemia.[1] Other researchers have suggested BS >144 mg/dL; BS >178 mg/dL plus glucosuria; a single reading of BS >239 mg/dL; or 2 consecutive levels of BS >216 mg/dL during a 4 hour period to define hyperglycemia. However, most neonatologists consider BS >180–200 mg/dL as an indication for therapeutic intervention.[2]

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The prevalence of hyperglycemia in neonates has been estimated as 20%–88%; wide variations in the reported prevalence result from differing definitions, varying birth weights (BW), degree of stress, and volume and rate of intravenous infusions of dextrose water (DW) in studied newborns.[2–5] Some studies have reported figures of 80% with BW <750 g, 72% with BW <1000 g, 68% with BW between 1000–1500 g and ≤5% in full term neonates.[6]

Predisposing factors for neonatal hyperglycemia include low birth weight, low gestational age, severeity of underlying disease, sepsis, hypoxia, low APGAR scores, surgery and stress. In additon, administration of the following medications results in an increased risk of hyperglycemia: rapid infusions of intravenous dextrose, intralipid solution, inotrope drugs, theophylline and steroids for Chronic lung Disease (CLD).[7–9]

Hyperglycemia causes an osmotic diuresis resulting in dehydration; other associated findings include;late-onset sepsis (LOS), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and prolonged hospitalization.[2,3,10–12]

This study was conducted to determine the risk factors, prevalence, and complications associated with hyperglycemia in VLBW neonates admitted to our NICU.

Materials and Methods

All VLBW infants admitted to the NICU of the Mahdieh Medical Center (a tertiary level university hospital with 39 NICU beds and around 5000 deliveries/year, perinatal center, located in south of Tehran, I.R. Iran, Shahid Beheshti University of Medical Sciences), during the study period of 3 years, from April 2009 to 2011 were eligible for inclusion. Information relevant to the study was extracted from the case notes and documented; this included demographic data, peri- and postnatal, specifics including maternal co-morbidities, pre-or postnatal steroid administration, gestational age, birth weight, sex, APGAR scores at 1 and 5 minutes, final diagnosis, (sepsis/RDS/etc.) hospital course and appearance of any complications viz. NEC, IVH etc. All medications administered during the hospital stay were also documented. Neonates with major congenital anomalies, chromsomal abnormalities and severe asphyxia were excluded from this study.

Intravenous infusion of DW 10% (5–8 mg/k/min) had been started for all VLBW neonates on admission to the NICU. Aminoacid infusion was started on day 2 and Intralipid on the 3rd day, if BS>150 mg/dl, considered as hyperglycemia and with BS >180–200 mg/dL, D/W10% was tapered to D/W 7.5% and then to DW 5% (4–6 mg/k/min) in the advent of hyperglycemia. However, if decreasing the rate of IV dextrose was not accompanied by a concomitant fall in BS and a reading of BS rise to >250–300 mg/dL, then bolus doses of subcutaneous/IV insulin, (0.05-0.1 units/kg/dose) were administered every 4–6 hours, until BS level fell to <200 mg/dL.[5,13,14] We did not use continuous insulin infusion due to the risk of hypoglycemia and limited number of nurses in our NICU.

BS was initially checked every 1–2 hours and, as the level dropped, every 4 hours until the reading was stable at normal levels. The duration of hyperglycemia and the details of the therapeutic intervention were recorded.

We described most of studied variables by counts and percentages and continuous variables by means and standard deviations. Association of each variable to hyperglycemia was assessed by simple and multiple logistic regression (using the Enter method) and unadjusted and adjusted odds ratios (ORs) were reported, respectively. Due to the presence of numerous variables in the model, some, such as APGAR-5'and mechanical ventilation ± surfactant, were removed due to co-linearity. *P*-values less than 0.05 were considered as statistically significant.

Results

Five hundred and sixty four VLBW newborns were included. The mean birth weight was 1179.26 ± 258.45 grams and the mean gestational age 29.68 ± 2.577 weeks; 51.2% were males and 73.8% were delivered by Caesarean section.

Hyperglycemia (BS >150 mg/dL) occurred in 179 VLBW (31.7%) with a mean BS of 397.76 mg/dL; 61.5% of them were during the 1st 24 hours after birth, 84.9% during the 1st week and 15.1% after the first week.

Hyperglycemia resolved during 72 hours in 99.4% of infants but persisted for >72 hours in 1 baby. Out of 179 neonates with hyperglycemia, 48 infants (26.8%) were given insulin; single bolus dose was required in 54.2%, and 2 doses for 27% and >3 doses in 17.8%. Insulin administration was not needed for >2 days of hospital course in any newborn (Tables 1 and 2).

Unilateral analysis revealed a strong relationship between hyperglycemia and the following factors: low gestational age (OR = 4.07, 95% CI = 2.09 – 7.93, $P < 0.001$) and ELBW (OR = 5.97, 95% CI = 3.77–9.44, $P < 0.001$). Other factors were: dopamine administration (OR = 2.19, 95% CI = 1.32 – 3.65, $P = 0.003$); intralipid (OR = 1.52, 95% CI = 1.04 – 2.22, $P = 0.03$); low APGAR at 5 minutes (OR = 4.44, 95% CI = 2.48–7.94, $P < 0.001$); RDS (OR = 4.20, 95% CI = 2.55–6.93, $P < 0.001$); complications of RDS, i.e., mechanical ventilation (MV), pneumothorax, pulmonary hemorrhage (PH) and CLD, were all independently associated with hyperglycemia (Table1).

In sub-group analysis significant association was found between hyperglycemia and the following factors: IVH >grade II (OR = 2.88, 95% CI = 1.28–6.49, $P = 0.01$); hospital stay more than 28 days in survivors (OR = 3.56, 95% CI = 2.02–6.25, $P < 0.001$); mortality (OR = 4.42, 95% CI = 3.00 – 6.52, $P < 0.001$), and ROP ≥ stage II in surviving neonates (OR = 2.05, 95% CI = 1.11–3.78, $P = 0.02$) (Tables 3 and 4).

Discussion

Multiple factors are involved in development of hyperglycemia in neonates; its prevalence increases with decreasing gestational age and birth weight, with the highest prevalence in ELBW infants.[15]

The following factors have been implicated in development of hyperglycemia[16]: 1) Infusion of IV dextrose > 4–7mg/kg/min, 2) Insufficient decrease in glucogenesis despite infusions of dextrose, 3) Lack of sufficient insulin dependent tissues (fat and muscle) in preterm neonates, 4) Inadequate insulin secretion in response to blood sugar levels, 5) Release of counter regulatory hormones like catecholamine and steroids in response to stress.

Reported prevalence of hyperglycemia, (BS > 150 mg/dL) varies widely from one study to another, e.g ; 2.9% from India,[17] and 13.9% from Turkey[18]; other studies give figures of approximately 20.67% in VLBW newborns and 60.88% in ELBW infants,[6–8,13] but in our study, theses were 31.7% and 54.4%, respectively.

In our study, hyperglycemia was found to be associated with various independent and inter-dependent factors such as gestational age below 28 weeks, birth weight under 1250 g, APGAR score below 6 at 5 minutes, advanced resuscitation and RDS along with its complications. All of these factors cause release of stress hormones, which forms the pathogenesis of hyperglycemia in them.

Additional associated factors in our neonates with hyperglycemia included administration of intralipid or dopamine; the former may act through insulin sensitivity disturbance and increasing the substrate for glucogenesis and the latter by reducing insulin secretion and increasing insulin unresponsiveness. These findings were similar to reports from Beardsall,[3] Zarif,[19] Lilien,[20] and Soghier.[21] Other authors have also reported association of hyperglycemia with sepsis, NEC, administration of theophylline and phenytoin, which were not seen in this study.[21,22]

The outcome of hyperglycemia is related to gestational age, maximum sugar level and severity of underlying illness in which case, management of the underlying disease takes preference over attempts to keep the blood glucose level within normal limits.[4] In our study, RDS affected 158 (88.3%) hyperglycemic neonates, and was the most common underlying disease. Treatment modalities which increase the risk for hyperglycemia (and also indicate the severity of the RDS) were mechanical ventilation (10.6%),

Table 1. Demographic data and risk factors of very low birth weight infants with and without hyperglycemia

Characteristic		With hyperglycemia (*n* = 179)	Without hyperglycemia (*n* = 385)	Unadjusted OR	95% CI	*P*-Value	Adjusted OR	95%CI	*P*-Value
sex	Female	82(29.93%)	192(70.07%)	1			1		
	Male	97(33.45%)	193(66.55%)	1.18	0.82–1.68	0.37	1.14	0.75–1.74	0.54
Birth weight (g)	1251–1500	44(16.67%)	220(83.33%)	1			1		
	1001–1250	55(35.95%)	98(64.05%)	2.81	1.77–4.46	<0.001	1.76	1.02–3.05	0.04
	≤1000	80(54.42%)	67(45.58%)	5.97	3.77–9.44	<0.001	2.72	1.39–5.3	0.003
Gestational age	>32 w	13(19.40%)	54(80.60%)	1			1		
	29–32 w	69(22.92%)	232(77.08%)	1.24	0.64–2.4	0.53	0.71	0.31–1.61	0.41
	≤28 w	97(49.49%)	99(50.51%)	4.07	2.09–7.93	<0.001	0.57	0.22–1.48	0.25
Delivery type	NVD	62(41.89%)	86(58.11%)	1			1		
	C/S	117(28.13%)	299(71.88%)	0.54	0.37–0.8	0.002	0.78	0.47–1.29	0.33
APGAR /1′	≥6	93(23.97%)	295(76.03%)	1			1		
	<6	86(48.86%)	90(51.14%)	3.03	2.08–4.42	<0.001	1.59	0.93–2.71	0.09
APGAR/ 5′	≥6	144(28.29%)	365(71.71%)	1			1		
	<6	35(63.64%)	20(36.36%)	4.44	2.48–7.94	<0.001	1.49	0.67–3.32	0.33
Intubation	yes	40(57.97%)	29(42.03%)	3.53	2.11–5.92	<0.001	1.17	0.55–2.49	0.69
	no	139(28.08%)	356(71.92%)	1			1		
Amino Acid	yes	165(31.67%)	356(68.33%)	0.96	0.49–1.87	0.90	1.36	0.57–3.22	0.49
	no	14(32.56%)	29(67.44%)	1			1		
Intra Lipid	yes	65(38.24%)	105(61.76%)	1.52	1.04–2.22	0.03	1.13	0.68–1.86	0.64
	no	114(28.93%)	280(71.07%)	1			1		
Aminophylline	yes	128(33.95%)	249(66.05%)	1.37	0.93–2.02	0.11	1.15	0.66–1.99	0.62
	no	51(27.27%)	136(72.73%)	1			1		
Dopamine	yes	33(47.83%)	36(52.17%)	2.19	1.32–3.65	<0.001	0.71	0.38–1.34	0.30
	no	146(29.49%)	349(70.51%)	1			1		
RDS	yes	158(39.01%)	247(60.99%)	4.20	2.55–6.93	<0.001	1.57	0.56–4.38	0.39
	no	21(13.21%)	138(86.79%)	1			1		
pneumothorax	yes	28(49.12%)	29(50.88%)	2.28	1.31–3.96	<0.001	0.90	0.46–1.78	0.77
	no	151(29.78%)	356(70.22%)	1			1		
Chronic lung disease	yes	47(45.63%)	56(54.37%)	2.09	1.35–3.24	0.001	1.37	0.72–2.58	0.33
	no	132(28.63%)	329(71.37%)	1			1		
Pulmonary hemorrhage	yes	46(50.00%)	46(50.00%)	2.55	1.62–4.02	<0.001	0.98	0.54–1.76	0.94
	no	133(28.18%)	339(71.82%)	1			1		
DIC[1] and/or Sepsis	yes	8(36.36%)	14(63.64%)	1.24	0.51–3.01	0.63	0.54	0.18–1.58	0.26
	no	171(31.55%)	371(68.45%)	1			1		
NEC	yes (≥Grade2)	2(33.33%)	4(66.67%)	1.08	0.2–5.93	0.93	1.28	0.15–11.22	0.82
	no	177(31.72%)	381(68.28%)	1			1		
Seizure	yes	55(57.89%)	40(42.11%)	3.83	2.42–6.04	<0.001	1.87	1.08–3.24	0.03
	no	124(26.44%)	345(73.56%)	1			1		
GI.Bleeding[2]	yes	20(54.05%)	17(45.95%)	2.72	1.39–5.34	0.004	1.45	0.67–3.12	0.35
	no	159(30.17%)	368(69.83%)	1			1		
Hematologic complications (Anemia, leukopenia, thrombocytopenia)	yes	108(35.88%)	193(64.12%)	1.51	1.06–2.17	0.02	1.18	0.74–1.87	0.49
	no	71(27.00%)	192(73.00%)	1			1		

[1]DIC = disseminated Intravascular Coagulation; [2]G.I.B = gastrointestinal bleeding

non-invasive ventilation (54.7%) and surfactant replacement (66.5%).

In contrast to some other reports,[6] no significant relationship was found between the incidence of hyperglycemia and the rate of glucose infusion in our study. Dweck et al., had observed occurrence of hyperglycemia even with low rates of glucose infusion.[23] In view of these findings, physicians need to recognize that additional factors besides rate of IV dextrose may play a major role in development of hyperglycemia.

Decreasing the rate of IV dextrose with simultaneous administration of aminoacids and intralipids has been advised in hyperglycemic neonates; however, no consensus exists about the degree of reduction; concentrations of DW 2.5%–5% are the minimal recommended values, but these rates would result in insufficient caloric intake. Therefore, some researchers have suggested that the dextrose infusions should continue at 4–6 mg/Kg/min and

Table 2. Characteristics of hyperglycemic newborns with insulin therapy

Characteristics		Total hyperglycemic newborns (n = 179)	With insulin (n = 48)	Without insulin (n = 131)
Sex	Female	82 (45.8%)	20 (41.7%)	62 (47.3%)
	Male	97 (54.2%)	28 (58.3%)	69 (52.7%)
Birth weight (g)	1251–1500	44 (24.6%)	1 (2.1%)	43 (32.8%)
	1001–1250	55 (30.7%)	9 (18.8%)	46 (35.1%)
	751–1000	50 (27.9%)	21 (43.8%)	29 (22.1%)
	≤750	30 (16.8%)	17 (35.4%)	13 (9.9%)
Gestational age (w)	>28	82 (45.8%)	6 (12.5%)	76 (58%)
	≤28	97 (54.2%)	42 (87.5%)	55 (42%)
Age of Hyperglycemia	<12 hr	58 (32.4%)	21 (43.8%)	37 (28.2%)
	13–24 hr	52 (29.1%)	17 (35.4%)	35 (26.7%)
	2–7 day	42 (23.5%)	9 (18.8%)	33 (25.2%)
	>7 day	27 (15.1%)	1 (2.1%)	26 (19.8%)
Duration of Hyperglycemia	≤72 hr	178 (99.4%)	47 (97.9%)	131 (100%)
	>72 hr	1 (0.6%)	1 (2.1%)	0 (0%)
Age of Insulin administration	No insulin	131 (73.2%)	0 (0%)	131 (100%)
	<12 hr	9 (5%)	9 (18.8%)	0 (0%)
	13–24 hr	16 (8.9%)	16 (33.3%)	0 (0%)
	2–7 day	18 (10.1%)	18 (37.5%)	0 (0%)
	>7 day	5 (2.8%)	5 (10.4%)	0 (0%)
Frequency of Insulin administration	No insulin	131 (73.2%)	0 (0%)	131 (100%)
	1 Dose	26 (14.5%)	26 (54.2%)	0 (0%)
	2 Dose	13 (7.3%)	13 (27.1%)	0 (0%)
	≥3 Dose	9 (5%)	9 (18.8%)	0 (0%)
Initial serum (Dextrose Water)	10%	124 (69.3%)	23 (47.9%)	101 (77.1%)
	7.5%	18 (10.1%)	7 (14.6%)	11 (8.4%)
	5%	35 (19.6%)	18 (37.5%)	17 (13%)
G.Peak (Maximum Glucose) mg/dL	Minimum	180.0	301.0	180.0
	Maximum	957.0	940.0	957.0
	Mean	398.8	532.7	349.7
	Median	370.0	522.0	331.0
	Standard Deviation	152.3	144.7	123.0
Phenytoin	yes	10 (5.6%)	4 (8.3%)	6 (4.6%)
	no	169 (94.4%)	44 (91.7%)	125 (95.4%)
Any respiratory support: NCPAP[1], NIV[2], INSURE[3], MV ± Surfactant	yes	162 (90.5%)	48 (100%)	114 (87%)
	no	17(9.5%)	0(0%)	17(13%)
RDS	yes	158 (88.3%)	47 (97.9%)	111 (84.7%)
	no	21(11.7%)	1(2.1%)	20(15.3%)
Sepsis	yes	4 (2.2%)	1 (2.1%)	3 (2.3%)
	no	175 (97.8%)	47 (97.9%)	128 (97.7%)
IVH (>Grade2)	yes	14 (7.8%)	1 (2.1%)	13 (9.9%)
	no	165 (92.2%)	47 (97.9%)	118 (90.1%)
ROP (in survivors)	yes	22 (25%)	2 (28.6%)	20 (24.7%)
	no	66 (75%)	5 (71.4%)	61 (75.3%)
ROP (Stage ≥ 2; in survivors)	yes	19 (21.6%)	2 (28.6%)	17 (21%)
	no	69(78.4%)	5(71.4%)	64(79%)
Outcome	Survive	88 (49.2%)	7 (14.6%)	81 (61.8%)
	Expire	91 (50.8%)	41 (85.4%)	50 (38.2%)

[1]N,CPAP = Nasal Continuous Positive Airway Pressure. [2]NIV = Non Invasive Ventilation, [3]INSURE = Intubation Surfactant Extubation.

early insulin therapy should be instituted to mange hyperglycemia. However, this approach would result in increasing the risk of hypoglycemia and neonatal mortality, so it has not been adopted in practice.[8,24,25] Recent recommendations include administering insulin as a bolus dose if the BS rises to 250–300 mg/dL. Therefore, the neonates receive sufficient glucose and calories from non-protein sources with satisfactory weight gain.[16,26] In our study, we implemented this intervention for 48 neonates with a mean BS of 532.7 mg/dL (range; 301–940 mg/dL) and hyperglycemia was controlled.

Insulin therapy did not have an effective change in morbidity and mortality of hyperglycemia infants in previous studies.[16,24,26,27] It is not clear whether increasing morbidity and mortality is related to hyperglycemia or its treatment. Therefore, this issue needs further investigation, but in our study administration of insulin revealed a significant association with neonatal death (85.4%). Most deaths were attributed to respiratory failure or sepsis due to shortcomings in equipment (high frequency ventilation, inhaled nitric oxide, extracorporeal membrane oxygenation, nurse to neonates ratio, fair control of nosocomial infection). (Table 2).

Our findings revealed association of hyperglycemia with increased duration of hospitalization, IVH > grade II and neonatal mortality, which is comparable to other reports (Table3).[2,3,17,21,24,27]

Finally, the hot topic of hyperglycemia is its relation to ROP,

Table 3. Complications in all VLBW infants with and without hyperglycemia

Characteristics		With hyperglycemia (*n* = 179)		Without hyperglycemia (*n* = 385)		OR	95%CI	*P*-Value
Severe IVH (>Grade2)	no	165	(92.18%)	374	(97.14%)	1		
	yes	14	(7.82%)	11	(2.86%)	2.88	1.28-6.49	0.01
ROP (all stage)	no	156	(87.15%)	337	(87.53%)	1		
	yes	23	(12.85%)	48	(12.47%)	1.04	0.61-1.76	0.90
Severe ROP (stage ≥ 2)	no	160	(89.39%)	347	(90.13%)	1		
	yes	19	(10.61%)	38	(9.87%)	1.08	0.61-1.94	0.78
Hospital Course (in survivors) (d)	≤28	18	(20.45%)	149	(47.76%)	1		
	>28	70	(79.55%)	163	(52.24%)	3.56	2.02-6.25	<0.001
Outcome	survive	88	(49.16%)	312	(81.04%)	1		
	expire	91	(50.84%)	73	(18.96%)	4.42	3.00-6.52	<0.001

Table 4. Risk of ROP in survives infants with and without hyperglycemia

Characteristics		With hyperglycemia (*n* = 88)		Without hyperglycemia (*n* = 312)		OR	95%CI	*P*-Value
ROP **(all stage)**	yes	22	(25.00%)	47	(15.06%)	1.88	1.06–3.34	0.03
	no	66	(75.00%)	265	(84.94%)	1		
Severe ROP **(≥stage II)**	yes	19	(21.59%)	37	(11.86%)	2.05	1.11–3.78	0.02
	no	69	(78.41%)	275	(88.14%)	1		

according to studies by Gary[12] and Ertl[28], the following findings are noticeable: 1) common risk factors, 2) increase in ROP after 1970 when dextrose administration became universally applied, 3) incidence of ROP was higher in neonates with hyperglycemia, 4) prevalance of ROP was higher in neonates with daily BS > 150 mg/dL, 5) ROP was 170% higher if recieving daily dextrose increased 10 mg/dL on average.

Although in our study, the incidence of ROP in all neonates (N = 179) was not significant (due to early death before ophthalmology examination for ROP), ROP ≥ stage II was significant in surviving neonates (Tables 3 and 4). Furthermore, among those who received insulin (N = 48), only 7 newborns survived, 2 (28.6%) of whom developed ROP that was treated by laser (Table2). Therefore, these results raise the question that if our neonates survived (especially those who received insulin), up to the age for ROP examination, the relation between hyperglycemia and ROP in our study was not more significants?! We need more studies to reach the definite evidence for this relation..

Our limitation in this study was high mortality rate (50.84%) of hyperglycemia infants,which interferes with accurate evaluation of hospital course and complications in our neonates.

Conclusion: Our findings revealed that hyperglycemia is prevalent in VLBW neonates and is associated with IVH, ROP in survived neonates, prolonged hospitalization and risk of mortality. These findings underscore the need for prompt diagnosis and appropriate management.

Acknowledgment

We thank the director and the personnel of Pediatric Infections Research Center for their support in implementation of this study. We also thank all our colleagues, (physicians, nurses and other personnel) in the New Born Service of Mahdieh hospital for their help in caring for the patients, collection and documentation of data, and advising the study team.

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