

Lactate As an Alternative Cerebral Fuel in Hypoglycemic Newborns

Amira Oshi¹, Omer Abdelbasit¹, Zain Seidahmed¹, Khalid AL. Hussein¹, Abeer Miqdad¹, Mohsen ALsamadi¹, Abdullah Alfari¹, Mosleh Jabari², Hassan Alshehri², Gehan Farid¹, Sohyma khalid¹, Fahad Al-Qashar³, Waad Almotairi¹

¹Department of Pediatrics, Neonatology division, Security Forces Hospital, Riyadh, Saudi Arabia.

²Department of Pediatrics, College of Medicine, Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

³Department of Pediatrics, Bahrain defence force Hospital, Royal Medical Services, Kingdom Of Bahrain
a_oshi@hotmail.com

Abstract: Objectives: Since blood glucose tends to fall physiologically in newborns in the first two hours of life, this fall might be exaggerated in babies who are at risk of developing hypoglycemia. Thus, measurement of blood glucose and serum lactate at the age of two hours may provide an idea about the response of those at risk of hypoglycemia compared to those with no risk of hypoglycemia. We measured serum lactate and glucose levels in term infants of diabetic mothers (IDM) and small for gestational age (SGA) babies at 2 hours of age, and we compared them with term newborns with no risk of hypoglycemia. The aim of that is to assess whether lactate increases during hypoglycemic episodes. **Patients and Methods:** A prospective observational study was conducted in Security Forces Hospital Riyadh, Saudi Arabia in the period from October 2014 to September 2015. All term infants born to diabetic mothers and small-for-gestational age infants during that period were recruited. Term normal newborns with no risk of hypoglycemia born at the same period were used as controls. Plasma glucose and lactate were measured in venous samples taken at the age of two hours. Hypoglycemia was defined as a glucose level below 2.6 mmol/litre while lactate level of 0.5 – 2.2 mmol/l was considered as normal range. Babies with metabolic disorders, major congenital malformations or who sustained Intrauterine or extra uterine hypoxia were excluded from the study. **Results:** A total of 470 newborn infants were recruited into the study. Of these 214 Babies were normal babies with no risk of hypoglycemia. 232 babies were infants of diabetic mothers, 24 babies were small-for-gestational age. A total of 98 babies developed hypoglycemia; 39 babies were infants of diabetic mothers, 7 were small-for-gestational age and 52 were presumably normal babies. Infants of diabetic mothers and small-for-gestational age who developed hypoglycemia had a significantly high mean lactate level of 3.32 mmol/litre compared to a level of 2.92 mmol/litre in those who did not develop hypoglycemia. (p-value 0.004). In general lactate level was higher in most of the involved babies in our study when compared to the standard institutional laboratory reference range though it did not reach statistical significance. **Conclusion:** The finding of significant high serum lactate level in our hypoglycemic babies suggests that lactate may have been used as an alternative cerebral fuel in hypoglycemia. Further studies are needed in hypoglycemic babies to explore the neuroprotective alternative fuels used.

[Amira Oshi, Omer Abdelbasit, Zain Seidahmed, Khalid AL. Hussein, Abeer Miqdad, Mohsen ALsamadi, Abdullah Alfari, Mosleh Jabari, Hassan Alshehri, Jeehan Fareed, Sohyma khalid, Fahad Al-Qashar, Waad Almotairi. **Lactate As an Alternative Cerebral Fuel in Hypoglycemic Newborns.** *J Am Sci* 2018;14(1):41-44]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). <http://www.jofamericanscience.org>. 4. doi: [10.7537/marsjas140118.04](https://doi.org/10.7537/marsjas140118.04).

Keywords: Lactate; Alternative Cerebral Fuel; Hypoglycemic Newborn

1. Introduction:

Hypoglycemia is linked to poor neurological outcome. Babies who are liable to hypoglycemia compensate by using alternative cerebral fuels as Ketones and Lactate for neuro protection. The affinity of glial cells in the brain is higher for lactate and Ketones than for glucose which is known as glucose sparing. In the first two post- natal hours, blood glucose level will normally decline. As a counter regulatory effect, there will be a glucagon surge and mobilization of hepatic glycogen to facilitate transition. Because

hepatic glycogen is limited, gluconeogenesis must take over. Reduction of blood glucose in the first two hours leads to decrease in insulin and increase in ketone bodies, free fatty acids and lactate. Small for gestational age (SGA) infants with limited glycogen store and infants of diabetic mothers with hyperinsulinism are at higher risk of developing hypoglycemia in the immediate post-natal period.

2. Patients and Methods

A Prospective observational study was conducted at Security Forces Hospital, Riyadh, Saudi Arabia between October 2014 to September 2015. All term infants of diabetic mothers of either gestational or pregestational diabetes and (SGA) infants, born during the study period were recruited. Normal newborns infants with no risk factors of hypoglycemia, who were delivered at the same period, were included as a control group.

Exclusion criteria:

Newborns who sustained intra or extra uterine hypoxia and newborns with metabolic disorders or major congenital anomalies were excluded. Hypoglycemia was defined as plasma glucose concentration of less than 47 mg /dl (2.6 mmol/l). (1) Hyperlactatemia was defined as plasma lactate > 2.2 mmol/l (Normal = 0.5-2.2 mmol/l or 4.5-19.8 mg/dl).

Plasma glucose and lactate levels, were measured on venous sample at 2 hours of age using grey tubes with sodium fluoride (COBAS 8000) analyzer was used. The study was approved by Security Forces Hospital Ethical and Research Committee.

Statistical Analysis:

The data was analyzed using (SAS software, version 9.2), and were presented as number (percent), Mean, Median, SD and QRANGE. Groups were compared using Chi-Square and T-test.

3. Results:

A total of 470 babies were enrolled in the study. 232 babies were IDM and 24 were SGA. The control group was composed of 214 normal babies. The Mean glucose level was 3.33. The Mean Lactate level was 3.07.

Table-1: Characteristic of Babies Studied

Variable	Level	N = 470	%
GENDER	Male Baby	233.00	49.6
	Female Baby	237.00	50.4
GROUP VARIABLE	Diabetic mothers and SGA Normal	256.00	54.5
DIABETIC STATUS	GDM	220.00	94.8
	PREGESTATIONAL	12.00	5.2
DIABETES TREATMENT	On Diet	175.00	75.4
	Insulin	57.00	24.6
MODE OF DELIVERY	SVD	335.00	71.3
	VENTOSE:	13.00	2.8
	C section	122.00	26.0
IF_CS	Elective	60.00	49.2
	Emergency	62.00	50.8
BIRTH WEIGHT	Mean	3194.6	-
APGAR Score One minute	Mean	8.87 (7-10)	-
APGAR Score five minutes	Mean	9.75 (8-10)	-
GESTATIONAL WEEKS	Mean	39.09 (37-43)	-
GLUCOSE	Mean	3.33 (1.1-8)	-
LACTATE	Mean	3.07 (0.75-17.79)	-

98 babies of 470 developed hypoglycemia. Of When all infants with hypoglycemia (98 babies) these 98 babies: 39 were IDM, 7 were SGA, and 52 were compared to non-hypoglycemic (372 babies): were presumably normal babies. Glucose Mean in The Mean lactate level in non-hypoglycemic babies with hypoglycemia was 2.14 and Lactate Mean infants was (3.03), $p = 0.127$. was 3.20.

Table-2: Lactate Level In Hypoglycemic Compared To Non-Hypoglycemic Newborns

Covariate	Statistics	Level	GROUP		Parametric P-value*	Non-Parametric P-value**
			Hypoglycaemic Babies N=98	Normal Babies N=372		
GENDER		Male Baby	60 (25.75)	173 (74.25)	0.010	0.012
		Female Baby	38 (16.03)	199 (83.97)		
GROUP VARIABLE		Diabetic mothers and SGA Normal	46 (17.9)	210(82.03)	0.093	0.110
			52 (24.41)	162 (75.7)		
DIABETIC STATUS		GDM	36 (16.36)	184 (83.64)	0.436	0.430
		PREGESTINAL	3 (25)	9 (75)		
DIABETES TREATMENT		On Diet	26 (14.86)	149 (85.14)	0.163	0.220
		Insulin	13 (22.81)	44 (77.19)		

MODE OF DELIVERY		SVD	72 (21.49)	263 (78.51)		
		VENTOSE:	3 (23.08)	10 (76.92)	0.811	0.796
		C section	23 (18.85)	99 (81.15)		
IF_CS		Elective	14 (23.33)	46 (76.67)	0.213	0.252
		Emergency	9 (14.52)	53 (85.48)		
BIRTH WEIGHT	Mean		3067.92	3227.99	0.297	0.281
APGAR Score One minute	Mean		8.87	8.87	0.930	0.287
APGAR Score five minutes	Mean		9.65	9.78	0.065	0.420
GESTATIONAL WEEKS	Mean		39.07	39.1	0.849	0.864
LACTATE LEVEL	Mean		3.2	3.03	0.274	0.127

Out of the (214) normal infants, 52 infants level was (3.09), while in non-hypoglycemic infants it (24.3%) developed hypoglycemia. The Mean lactate was (3.17), $p = 0.295$.

Table-3: Lactate Level In Hypoglycemic Normal Newborns Compared To Non-Hypoglycemic

Covariate	Statistics	Level	GROUP		P-Parametric value*	P-Non-Parametric value**
			Hypoglycaemic Babies N=52	Normal Babies N=162		
GENDER		Male Baby	32 (29.63)	77 (70.64)	0.079	0.083
		Female Baby	20 (19.05)	85 (80.95)		
MODE OF DELIVERY		SVD	41 (26.45)	114 (73.55)	0.445	0.428
		VENTOSE	2 (25)	6 (75)		
		C section	9 (17.65)	42 (82.35)		
IF_CS		Elective	6 (22.22)	21 (77.78)	0.363	0.473
		Emergency	3 (12.5)	21 (87.5)		
BIRTH WEIGHT	Mean		3183.38	3159.31	0.684	0.647
APGAR Score One minute	Mean		8.9	8.86	0.679	0.608
APGAR Score five minutes	Mean		9.79	9.74	0.501	0.532
GESTATIONAL WEEKS	Mean		39.4	39.37	0.877	0.945
LACTATE LEVEL	Mean		3.09	3.17	0.697	0.295

Of (256) IDM and SGA infants, 46 (17.9 %) hypoglycemic infants was (3.32). Mean lactate level in developed hypoglycemia. Mean lactate level in non-hypoglycemic was (2.92) and $p = 0.004$.

Table-4: Lactate Level in Hypoglycemic IDM and SGA Compared To Non-Hypoglycemic

Covariate	Statistic s	Level	GROUP		P-Parametric value*	P-Non-Parametric value**
			Hypoglycemic Babies N=46	Normal Babies N=210		
GENDER		Male Baby	28 (22.58)	96 (77.42)	0.062	0.075
		Female Baby	18 (13.64)	114 (86.36)		
DIABETIC STATUS		GDM	36 (16.36)	184 (83.64)	0.436	0.430
		PREGESTATION	3 (25)	9 (75)		
DIABETES TREATMENT		On Diet	26 (14.86)	149 (85.14)	0.163	0.220
		Insulin	13 (22.81)	44 (77.19)		
MODE OF DELIVERY		SVD	31 (17.13)	149 (82.78)	0.892	0.830
		VENTOSE	1 (20)	4 (80)		
		C section	14 (19.72)	57 (80.28)		
IF_CS		Elective	8 (24.24)	25 (75.76)	0.372	0.390
		Emergency	6 (15.38)	32 (84.21)		
BIRTH WEIGHT	Mean		2937.39	3278.91	0.241	0.050
APGAR Score One minute	Mean		8.83	8.89	0.529	0.304
APGAR Score five minutes	Mean		9.5	9.8	0.007	0.079
GESTATIONAL WEEKS	Mean		38.7	38.88	0.278	0.272
LACTATE LEVEL	Mean		3.32	2.92	0.086	0.004

The outcome of (232) infants of diabetic mothers infants was (3.19). The Mean lactate level in nonshowed that (39) infants developed hypoglycemia hypoglycemic was (2.89) and $p = 0.022$. (16.8 %). The Mean lactate level in hypoglycemic

Table-5: Lactate Level in Hypoglycemic IDM Compared To Non-Hypoglycemic IDM

Covariate	Statistics	Level	GROUP		Parametric P-value*	Non-Parametric P-value**
			Hypoglycemic Babies N=39	Normal Babies N=193		
GENDER		Male Baby	23 (20.18)	91 (79.82)	0.178	0.219
		Female Baby	16 (13.56)	102 (86.44)		
DIABETIC STATUS		GDM	36 (16.36) 3 (25)	184(83.64) 9 (75)	0.436	0.430
		PREGESTATIONAL				
DIABETES TREATMENT		On Diet Insulin	26 (14.86)	149 (85.14) 44	0.163	0.220
			13 (22.81)	(77.19)		
MODE OF DELIVERY		SVD	30 (17.86)	138 (82.14)	0.736	0.636
		VENTOSE:	1 (20)	4 (80)		
		C section	8 (13.56)	51 (86.44)		
IF_CS		Elective	5 (17.86)	23 (82.14)	0.359	0.458
		Emergency	3 (9.68)	28 (90.32)		
BIRTH WEIGHT	Mean		3116.54	3369.69	0.438	0.180
APGAR Score One minute	Mean		8.82	8.92	0.300	0.204
APGAR Score five minutes	Mean		9.54	9.83	0.018	0.312
GESTATIONAL WEEKS	Mean		38.85	38.93	0.649	0.629
LACTATE LEVEL	Mean		3.19	2.89	0.215	0.022

4. Discussion:

The results showed that the lactate level was high in both hypoglycemic and non-hypoglycemic babies as compared to the standard laboratory reference range for the lactate ($p=0.127$). In infants of diabetic mothers and SGA infants with hypoglycemia, the lactate level was significantly higher when compared to the same group of infants who did not developed hypoglycemia ($p = 0.004$). This suggests that infants with hypoglycemia, in this group, tend to increase their plasma lactate level, most probably to be used as a cerebral source for energy. In a RCT by Harris et al., on newborns with hypoglycemia within the first 48 hours after birth, it was observed and suggested that lactate rather than ketones may provide an alternative cerebral fuel for neuroprotection. (2) Maran et al. in a study of hypoglycemia in adults, who were given intravenous lactate infusion to reach a mean plasma lactate concentration of 1.8 ± 0.1 mM, showed improvement in cerebral cognitive function, suggesting that lactate was a good provider as alternative cerebral fuel. (3).

Conclusion:

The finding of significant serum lactate level in our hypoglycemic babies, suggests that it tends to provide an alternative cerebral fuel. Further studies are needed in that aspect, both nationally and internationally since it can provide an accessible easy

way to prevent brain damage by hypoglycemia in the newborn.

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