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Is glycosuria a reliable indicator of adequacy of glucose infusion rate in preterm infants?

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ABSTRACT

Context: Adequacy of glucose infusion may be monitored via the glycosuria levels, as there is a relationship between glycemia and glycosuria regulated by the renal glucose threshold. In the neonatal period, however, this relationship is not so clear.

Objective: To evaluate the occurrence of glycosuria in preterm infants submitted to glucose infusion and to verify the relationship between glycosuria and blood glucose level.

Design: Accuracy study.

Setting: Neonatal intensive care unit of General Maternity Hospital.

Patients: 40 preterm newborns receiving glucose infusion.

Procedures: 511 concomitant determinations of glycemia and glycosuria were performed. These 511 pairs were divided into stable and unstable, according to the clinical status of the newborn at the time of data collection, and they were studied in relation to the gestational age, birth weight and glucose infusion rate.

Results: The results revealed a greater frequency of glycosuria in gestational age ≤ 30 weeks, birth weight <1500 g and glucose infusion rate > 6 mg/kg/min. Eight (25.8%) episodes of positive glycosuria occurred in the absence of hyperglycemia, indicating only a moderate concordance between them.

Conclusion: Glycosuria alone is an unreliable marker of blood glucose concentration and adequacy of glucose infusion rate. It is therefore necessary to monitor blood glucose levels in infants submitted to continuous glucose infusion.

Key words: Blood Glucose. Glycosuria. Hyperglycemia. Newborn Infant. Parenteral Infusion.

INTRODUCTION

There is at present great interest in adequate nutrition for newborns in neonatal intensive care units. Breast milk is the best food, but its use is not always possible. This impossibility has led to the development of parenteral nutrition. This type of nutrition has glucose as its basic component, which can provoke alterations in glycemic levels, especially in unwell newborn infants.

Hyperglycemia raises blood osmolarity and it can cause intracranial hemorrhage[1] and also promote glycosuria and dehydration.[1]

Adequacy of glucose infusion may be monitored via the glycosuria levels, as there is a relationship between glycemia and glycosuria regulated by the renal glucose threshold.

In the neonatal period, however, this relationship is not so clear because of the influence of gestational age, birth weight, glucose infusion rate and other special conditions that modify carbohydrate homeostasis. Compared to adults, the tubular reabsorption of glucose is diminished in the embryonic life of some animals.[2,3] Robillard et al[4] showed that in sheep embryos, the renal excretion of glucose is higher than in fully-grown animals.

Using alpha-metyl-glycopyroside, it was

possible to study glucose transportation in the embryo's kidney. Alpha-methyl-glycopyroside shares the carrier of glucose-D present in the proximal tubule membrane, without interfering in its transport system.[4] This transportation has been shown to be similar to that of the adult kidney and has also been shown to interact with sodium transportation.[5] This mechanism is cation-specific, electrogenic and pH sensitive,[6] being qualitatively similar to that of the adult. During hyperglycemic embryo states, glycosuria and osmotic diuresis appear, indicating that the physiopathology of glycosuria is the same in newborns and adults, appearing when the glucose renal excretion limit is exceeded.[7]

The renal excretion of glucose is higher in newborns with gestational age less than 34 weeks.[2] The glucose reabsorption fraction is 92.5% in these children, 99.2% in neonates between 34 and 37 weeks and 99.4% in full term newborns, justifying the higher frequency of glycosuria in more immature preterm newborns.[8,9] These newborns usually have a relatively lower glucose excretion limit and consequently, hyperglycemia easily induces glycosuria. But it is very difficult to determine the level of glycemia above which glycosuria will occur and how these preterm infants will react according to the various birth weights, gestational ages and differences in clinical conditions they face.[10]

In the light of these facts, the use of glycosuria to evaluate the adequacy of the glucose infusion rate in preterm newborns submitted to glucose infusion merits some criticism, since very few studies have emphasized the influence of the glucose infusion rate and clinical condition.[11]

The objectives of this study were to evaluate the occurrence of glycosuria in preterm infants submitted to glucose infusion and to verify the relationship between glycosuria and blood glucose level.

METHODS

This prospective research was developed in the Neonatal Iintensive Care Unit of Santa Catarina Maternity Hospital (São Paulo, Brazil), a private hospital which attends to middle class mothers. The protocol was approved by the Hospital Ethics Committee and all newborns were included after consent from their parents.

From January 1st to December 31st, 1994, 40 preterm newborn infants were studied, selected through routine tracking in the Nursery, who required glucose infusion in the first week of life.

Prematurity was defined as a gestational age of less than 37 weeks, in accordance with the date of the last menstruation of the mother. In the absence of this information, ultrasonographic evaluation and also the Dubowitz Method were used.[12,13] The preterm newborns were classified by size as small, adequate or large, according to a birth curve developed in the city of São Paulo and adopted by this Service.[14]

All of these 40 preterm newborn infants had their qualitative glycosuria and blood

Table 1 - Distribution of glycosuria episodes in Groups I and II, according to gestational age (GA), birth weight (BW) and glucose infusion rate (GIR).

	Glycosuria episodes					
	GA (weeks)		BW (g)		GIR (mg/kg/min)	
	≤30	>30	<1500	≥1500	≤6	>6
	n(%)	n (%)	n (%)	n (%)	n (%)	n (%)
Group I	4 (23.5)	5 (35.7)	3 (18.7)	6 (40.0)	5 (35.7)	4 (23.5)
Group II	13 (76.5)*	9 (64.3)	13 (81.3)*	9 (60.0)	9 (64.3)	13 (76.5)*
Total	**17(100.0)**	**14(100.0)**	**16(100.0)**	**15(100.0)**	**14(100.0)**	**17 (100.0)**

** p<0.05*

glucose level determined concomitantly. Immediately after the collection of the urine sample, the blood for glycemia dosage was obtained. At least three daily determinations of the glycemia and glycosuria pair were accomplished.

The glycemia and glycosuria pairs were divided into two groups, according to the clinical and laboratorial characterization of the clinical status at the time of the data pair collection: Group I (stable clinical moment) and Group II (unstable clinical moment). The objective of this characterization was to put a value on the existence of stability in the mechanisms responsible for the glucose homeostasis at the time of determination of the pair.

Preterm infants in the "stable clinical moment" group presented stable body temperature, satisfactory hemodynamic and respiratory conditions, neurological exam appropriate for the getational age, normal abdominal propedeutics and successfully receiving enteral nutrition.

While in respiratory assistance, the following clinical and laboratorial parameters were valued for "stability", in addition to the elements referred to above: respiratory frequency < 60 movements/min; heart frequency between 100 and 160 beats/min; average arterial pressure between 45 and 60 mmHg; O_2 saturation³ 92% (pulse oximetry); pH between 7.25 and 7.45; paO_2 > 60 mmHg, $paCO_2$ < 45 mmHg and diuresis³ 1 ml/kg/h.

The clinical "moments" that did not fulfill the criteria mentioned above were considered unstable.

The site for capillary blood collection was the sole of the heel (3 heparinized capillary tubes - 240 ml). The determination of blood glucose was performed via the glucose oxidase colorimetric method and readings were taken until 30 minutes after the collection.[15] The hyperglycemia was defined as glucose blood concentration superior to 125 mg/dl.[16,17] This value corresponds to a plasma glucose concentration of 150 mg/dl.[16,17]

A urine sample was collected (minimum volume of 1ml) to determine glycosuria, via a collecting bag fixed to the genitalia.[15] The technique for determining the qualitative glycosuria consisted of the same biochemical method as for blood glucose.[18] Glycosuria determinations from the first 12 hours of life were excluded, as this urine could be mixed with the fetal.[19]

Statistical Methods. To evaluate the glycosuria and its relation to the glycemic levels, a database was built up, pairing the simultaneous measures of glycemia and glycosuria. These pairs were divided according to: birth weight, gestational age, glucose infusion rate and the clinical "moment" (stable or unstable). The McNemar Chi-square test and Kappa statistics were used for verifying the conformity between the paired measurements, i.e. the presence of hyperglycemia and its agreement with the presence of glycosuria. The Chi-Square test was used for the comparison of proportions. In all of the tests, the 0.05 level of significance was adopted.

RESULTS

The population consisted of 40 preterm infants, 23 male (57.5%) and 17 female

Table 2 - Distribution of glycosuria episodes, according to the presence of hyperglycemia in Groups I and II

Glycosuria	Hyperglycemia	Group I n (%)	Group II n (%)	Total n (%)
+	+	8 (34.8)	15 (65.2)	23 (100.0)
+	-	1 (12.5)	7 (87.5) *	8 (100.0)
-	+	9 (50.0)	9 (50.0)	18 (100.0)
-	-	210 (54.6)	252 (54.4)	462 (100.0)
Total		**228 (44.6)**	**283 (55.4)**	**511 (100.0)**

** p <0.05*

(42.5%). Their birth weights varied from 820 to 2490 g (average: 1846.5 g). The gestational age varied between 28 and 36 weeks (average: 34.43 weeks); 28 infants were of adequate size for the gestational age (70.0%) and 12 infants were small for the age (30.0%).

A total of 511 concomitant determinations of glycemia and qualitative glycosuria were performed in the first week of life (average: 12.8 per newborn): 228 (44.6%) in Group I and 283 (55.4%) in Group II. From these, 59 (11.5%) episodes of hyperglycemia, 14 (2.7%) of hypoglycemia and 438 (85.8%) of normal glycemia were obtained. Glycosuria was positive in 31 (6.1%) determinations, 9 (29.1%) in Group I and 22 (70.9%) in Group II ($p < 0.05$).

Table 1 exhibits the distribution of the variables studied in both groups: gestational age (≤30 and >30 weeks), birth weight (<1500 and[3] 1500 g) and glucose infusion rate (≤6 and >6 mg/kg/min).

The distribution of concordance observed between hyperglycemia and glycosuria in the two groups is presented in Table 2.

For the analysis of glycemic levels for predicting glycosuria, two cut-off points for glycemia were evaluated: glycemia >125 mg/dl (this level was adopted to define hyperglycemia), and glycemia >150 mg/dl. Comparison of the discordant pairs hyperglycemia with glycosuria absent and normoglycemia with glycosuria present was done, as shown in Table 3.

DISCUSSION

In this analysis of the renal excretion of glucose in preterm newborn infants with supposed normal renal function, considering the differences in maturity, birth weight, glucose infusion rate, glycemia and clinical condition, glycosuria was positive in 31 (6.1%) episodes and it was significantly more frequent at a gestational age ≤30 weeks, birth weight <1500 g and glucose infusion rate >6 mg/kg/min ($p<0.05$) (Table 1).

The urinary concentration of glucose in full-term infants is slightly higher than in older children and adults. In infants below 32 weeks of gestational age, it is even higher.[20] The higher frequency of glycosuria at lower gestational ages and birth weights is directly linked to immaturity, since nephrogenesis is completed around 34 weeks of gestation and, in more premature newborns, glycosuria appears at lower glycemia levels.[20] Regarding the glucose infusion rate, as it is a predictor of hyperglycemia, it may be supposed that the higher it is, the higher the glycosuria frequency will be.[11]

Comparing groups I and II, it could be observed that the episodes of glycosuria were strongly associated to clinical instability at the time of sample collection ($p<0.05$). The episodes of glycosuria without hyperglycemia were also associated significantly with the clinical moment ($p<0.05$). Therefore, greater attention should be given to the presence of glycosuria without hyperglycemia, as it was observed in only one episode in Group I and in 7 in Group II (Table 2).

Temporary variations of the renal blood flow in unstable clinical conditions or in unwell preterm newborn infants could presumably influence the renal excretion of glucose, even if alterations in renal function were not detectable.

In order to establish whether there is a

Table 3 - Different cut-off points for glycemia, comparing discordant pairs, using McNemar Chi-square test and Kappa statistics.

Cut-off points	Chi-square	Co-positivity (%)	Co-negativity (%)	Kappa Statistics
glycemia > 125 mg/dl	16.6*	39.9	98.2	0.46 **
glycemia > 150 mg/dl	6.9*	77.8	96.5	0.55 **

**p<0.05 **moderate conformity*

concordant relationship between the glycemic levels and the presence of glycosuria, the McNemar Chi-square test was used. The discordant pairs of hyperglycemia with glycosuria absent and normal glycemia with glycosuria present were studied. Two cut-off points were used: glycemia greater than 125 mg/dl and 150 mg/dl. With the first cut-off, 16.6% of discordance was observed ($p<0.05$), and with the second, this discordance reduced to 6.9%, but remained significant (Table 3). Another method to study the discordant pairs is via Kappa statistics, which evaluate their co-positivity and co-negativity. The same two cut-off points were used and for both of them the conformity was moderate, 0.46 and 0.55, respectively (Table 3).

From this result, showing only a moderate conformity between levels of glycemia and glycosuria, it is possible to say that hyperglycemia is neither the only variable nor the most important predictor of glycosuria. In the same way, glycosuria is not always an indicator of high glycemic level.

In healthy full-term infants with normal blood glucose levels, only traces of glucose are found in urine.[21] However, these values are unknown for unwell immature infants, in whom glycosuria may be observed even in conditions of normal glycemia.[22] In newborns with a gestational age of 29 weeks this limit is 152 ± 8 mg/dl of glycemia, confirming the greater glucose excretion in preterm infants.[23]

One explanation for these findings could be based on the concept of basal glycosuria, in which the excretion of endogenous glucose would not depend on the maximum value of the tubular reabsorption but would appear to be determined by the tubular flux.[21]

Increased excretion of glucose in preterm newborns with sepsis, intracranial hemorrhage and serious respiratory distress has been demonstrated.[11] These results suggest that clinical instability, together with immaturity, could contribute to the diminished tubular reabsorption of glucose.[11]

The relationships observed in our study between glycemic levels and glycosuria suggest that the clinical instability of the newborn was a relevant factor in the genesis of glycosuria, followed by glucose infusion, gestational age and birth weight. The presence of hyperglycemia was not shown to be essential for glycosuria, demonstrating that this cannot be used as a unique parameter in the evaluation of glucose infusion rate adequacy.

The practical significance of this work is that glycosuria alone is an unreliable marker for blood glucose concentration and forglucose infusion adequacy. It is therefore necessary to monitor blood glucose levels in infants who are on continuous glucose infusion.

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RESUMO

Objetivos: Avaliar a ocorrência de glicosúria em recém-nascidos pré-termo submetidos à infusão parenteral de glicose e verificar a relação entre glicemia e glicosúria.
Metodologia: Foram realizadas 511 determinações concomitantes de glicemia e glicosúria em 40 recém-nascidos pré-termo recebendo infusão parenteral de glicose. Estes 511 pares foram dicotomizados conforme o "momento" clínico do recém-nascido no instante da coleta, em estáveis e instáveis, e estudados em relação à idade gestacional, peso de nascimento e velocidade de infusão de glicose.
Resultados: Os resultados revelaram maior frequência de glicosúria em idade gestacional £ 30semanas, peso de nascimento < 1500g e velocidade de infusão de glicose > 6mg/kg/min. Houve a ocorrência de 8 (25,8%) episódios de glicosúria positiva na ausência de hiperglicemia mostrando somente uma concordância moderada entre os dois fenômenos.
Conclusões: A glicosúria não deve ser utilizada como indicadora de níveis glicêmicos nem de adequação da taxa da infusão de glicose. É necessário, portanto, a monitorização frequente da glicemia em recém-nascidos pré-termo submetidos à infusão de glicose.