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Original Article

Assessment of the Relationship between Hyperglycemia during the First 24 Hours Post-surgery and the Type of Calorie Intake in the Neonatal Intensive Care Unit

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ABSTRACT

Background: The present study aimed to determine the mean blood glucose during the first 24 h post-surgery and its relation with the source of calorie intake.
Methods: The data of the current observational retrospective study was collected from hospital medical records. A total of 45 neonates suffering from atresia in different parts of the gastrointestinal tract, who were candidates for open abdominal surgery from September to October 2016 were selected. Blood glucose within 24 h after the surgery were taken four times using a glucometer. Moreover, the mean blood glucose during this period was calculated. Independent Student's t-test, chi-square test, and logistic regression model were performed to assess the association of post-operative blood glucose with calorie and macronutrient intakes.
Results: In one third of neonates, the mean blood glucose of the samples during the first day after the surgery was ≥180 mg/dl and the rest of them had mean blood glucose of 40-179 mg/dl. There was a significant relationship between blood glucose BG≥180 mg/dl and calorie ($P=0.001$), macronutrient (carbohydrate ($P<0.001$), and fat ($P=0.04$)) intakes. After adjustment of confounding variables, carbohydrate intake was found as an independent factor in increasing BG≥180 mg/dl during the first 24 h after the surgery ($P=0.01$). In addition, fat intake was observed as an effective factor in decreasing BG≥180 mg/dl during this time ($P=0.04$).
Conclusion: The present study revealed that there was a significant relationship between mean blood glucose during the first 24 h after the surgery and intake of macronutrients (carbohydrate and fat).

Keywords: Hyperglycemia, Macronutrients Intake, NICU, Post-surgery

Introduction

Surgery is a major cause of stress due to the disruption of homeostasis and physical balance (1). Several studies have shown that the mortality rate increases after the surgery in infants aged<30 days (2-5). Therefore, it is essential to determine the important post-surgery risk factors affecting treatment outcomes (6, 7).

Hyperglycemia is common in critically ill patients. Many factors cause hyperglycemia (e.g., high glucose injection, inability to uptake glucose, defect in the hormones regulating glucose, infection, respiratory distress, low birth weight, pain, duration of the surgery, calorie intake, and post-operation macronutrient intake)(8). High blood glucose after the surgery in newborns imposes risks of brain damage, growth retardation, and lack of acquiring mental skills in childhood (6).

A neonate requires 100-200 kcal/kg/day of energy for normal growth, 6-12 mg/kg/min of carbohydrate, 3 gr/kg/day of protein, and 4 gr/kg/day of fat(9). Since the growth process stops

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at metabolic stress, energy requirement reduces after the surgery (10, 11). It is recommended to take 60-70 kcal kg/day energy (13, 12), 4-8 mg/kg/min of 10% dextrose solution , 2 gr/kg/day of protein, and 1 gr/kg/day of fat (11, 14). Excessive feeding in this stage can lead to increased production of endogen fats (11, 15). Furthermore, prescription of excessive carbohydrates in this stage can increase blood fatty acids and produce fat (11, 15) resulting in fatty liver and increased ventilator dependence (16). Nutritional intervention for infants undergoing surgery should be performed to reduce surgery metabolic complications (8). The present study aimed to evaluate the clinical and nutritional factors associated with hyperglycemia after the surgery in full-term newborns.

Methods

This observational retrospective study is designed based on medical records. A total of 45 newborns in the neonatal intensive care unit (NICU) of Dr. Sheikh Hospital, Mashhad, Iran, who were candidates for open abdominal surgery due to atresia in different parts of the gastrointestinal tract were selected from September to October 2016. The infants with insulin injection need or metabolic disorders, such as diabetes mellitus, congenital hyperinsulinemia or any other underlying disease were excluded from the current study.

Blood glucose samples after the surgery had been taken by a glucometer (EasyGluco Plus; US Diagnostics, New York, NY) with an interval of 6 h and the results were recorded routinely. Four times interval was considered between each blood sugar sampling, except for the first 6 h immediately after the surgery.

Blood glucose of 180 mg/dl was regarded as cut-off of high blood glucose (17). Consequently, the patients were categorized into relatively normal blood glucose group (40-179 mg/dl) and high blood glucose group (≥180 mg/dl) (18, 19). None of the infants in the present study had blood glucose less than 40 mg/dl.

Based on the evidence, the birth weight was classified into two groups of normal with weight≥2.5 kg and lower than normal with weight<2.5 kg. The two groups were compared according to age at the time of surgery, gender, birth weight, and ventilator dependence (20).

In parenteral nutrition of these infants, combined dextrose solution, amino acid, and intralipid (5-10%, 10%, and 10%) were used, respectively. Dextrose, amino acid, and intralipid solutions were considered (3.4 kcal/ml, 4 kcal/ml, and 9 Kcal/ml), respectively. Then, the amount of calorie and macronutrient (carbohydrates, protein, and fat) intakes through parenteral nutrition were calculated based on the age at the time of the surgery and weight of each patient.

Calorie and macronutrient intakes for each infant were calculated and compared with the guideline's recommendation for energies (60-70 kcal/kg/day) and macronutrients (4-8 mg/kg/min of carbohydrate, 2 gr/kg/day of protein, and 1 gr/kg/day of fat) intake after the surgery (12, 13) and the collected data were stated as a percent of the standard intake. Thereafter, blood glucose groups were compared based on calories and macronutrients of their diet and the percentage of the standard calorie and macronutrient intakes.

Data analysis

Statistical analysis was performed using SPSS software (version 16). The collected data were described by frequency tables and mean indices. Independent student's t-test was used to investigate the relationship between the mean of high and relatively normal blood glucose with quantitative variables. In addition, a chi-square test was performed for qualitative variables. A logistic regression model was used for the adjustment of confounding variables in case of high blood glucose after the surgery. A p-value of less than 0.05 was considered statistically significant.

Results

Basic results

The demographic characteristics of the study population are shown in Table 1.

Table 2 represents the significant relationship between the mean of relatively normal and high blood glucose after the surgery and birth weight (P<0.001). There were 87.5% infants with

Table 1. Demographic data of 45 infants undergoing surgery

Age (day)		5.5±2.5 a
Gender	Male	22 (48.9) b
	Female	23 (51.1) b
Birth Weight		2.52±0.62 a
Birth Weight<2.5 kg		16 (35.6) b
Birth weight≥2.5 kg		29 (64.4) b
Mean blood sugar post-operation		161.55±40.9 a
Mean Blood Sugar=40-179 mg/dl		30 (66.7) b
Mean Blood Sugar≥180 mg/dl		15 (33.3) b
Ventilation	No	24 (53.3) b
	Yes	21 (46.7) b

a: Mean±SD
b: Number (percent)

hyperglycemia and birth weight<2.5 kg. However, no significant relationship was observed between the mean blood glucose after surgery and age, gender, and ventilator dependency.

A comparison of blood glucose groups based on calories and macronutrients intakes is demonstrated in Table 3. The results showed that the mean of calorie, carbohydrate, and protein intakes were higher in the hyperglycemic group than the relatively normal glycemic group. However, the mean of fat intake was higher in the relatively normal glycemic group than the hyperglycemic group. This difference between the groups in intakes of calorie, carbohydrate, and fat was significant (P=0.001, P<0.001, P=0.04), respectively; however, protein intake was not significantly different between the two groups.

In addition, it was observed that the hyperglycemic group received calorie, carbohydrate, and protein close to the optimal values, in the comparison of the percentage of intake from optimal values. This difference was significant between groups in calories and carbohydrate intakes (P=0.001, P<0.001), respectively. However, protein intake was not significantly different between the two groups, compared to the optimal values.

The obtained findings showed that although fat intake was close to the optimal values in the hyperglycemic group, it was 1.5 times higher than the optimal values in the relatively normal glycemic group, and this difference was significant between the two groups (P=0.04).

In order to predict the impact of the macronutrient intake (carbohydrate, protein, and fat) on blood glucose≥180 mg/dl, a logistic regression model was conducted. As it is demonstrated in Table 4, carbohydrate intake was considered an independent factor influencing the blood glucose≥180 mg/dl (P=0.01, 95% CI for EXP (B): 1.02-1.15). Furthermore, fat intake was regarded as an effective factor decreasing blood glucose to 180 mg/dl (P=0.04, CI for EXP (B): 0.87-0.99).

Table 2. Comparison of blood glucose groups based on age, gender, weight, and ventilator dependency

Mean Blood Sugar		40-179 mg/dl	≥180 mg/dl	p
Age (day)		5.30±2.68 a	5.93±2.28 a	0.43 b
Gender	Male	12 (54.5) c	10 (45.5) c	0.09 d
	Female	18 (78.3) c	5 (21.7) c	
Birth weight (kg)	<2.5	2 (12.5) c	14 (87.5) c	0.001 d
	≥2.5	28 (96.6) c	1 (3.4) c	
Ventilation	No	18 (75) c	6 (25) c	0.2 d
	Yes	12 (57.1) c	9 (42.9) c	

a: Mean±SD
b: Independent student's t-test
c: Number (percent)
d: Chi-square test
Bold value is statistically significant.

Table 3. Comparison of blood glucose groups based on calories and macronutrient intakes

	Mean blood sugar post-operation	40-179 mg/dl	≥180 mg/dl	p
TPN	Energy(kcal/kg/day)	52.56±13.88a	68.68±16.44 a	0.001b
	Carbohydrate (gr/kg/day)	7.39±1.67 a	12.65±3.12 a	<0. 001b
	Protein (gr/kg/day)	1.89±0.94 a	2.02±0.91a	0.6 b
	Fat(gr/kg/day)	1.71±1 a	1.1±0.76 a	0.04 b
Intake from Standard TPN (%)	Energy	80.86±21.35 a	105.67±25.3 a	0.001b
	Carbohydrate	62.93±14.25 a	107.67±26.63 a	<0. 001b
	Protein	94.79±47.44 a	101.23±45.75 a	0.6 b
	Fat	154.13±90.19 a	99.8±68.71 a	0.04b

a: Mean±SD
b: Independent student's t-test
TPN: Total parenteral nutrition
Bold values are statistically significant.

Table 4. Effect of macronutrients intake on blood glucose levels≥180 mg/dl

Macronutrients	p a	EXP(B)	95% C.I. for EXP(B)
Carbohydrate (gr/kg/day)	0.01	1.08	1.02-1.15
Protein (gr/kg/day)	0.42	0.95	0.86-1.06
Fat (gr/kg/day)	0.04	0.93	0.87-0.99

a: Logistic Regression model
EXP(B): the exponentiation of the coefficients
Bold values are statistically significant.

Discussion

The present study aimed to determine the relationship of post-surgical calorie and macronutrient intakes (carbohydrates, protein, and fat) with high blood glucose in the neonates admitted to the neonatal intensive care unit. To the best of the authors' knowledge, the current research was the first study which compared the value of macronutrient intake to optimal values through parenteral nutrition, and then evaluated the mean blood glucose after the surgery based on the obtained values.

To this date, there is no consensus agreement in determining the cut-off values of high blood glucose for infants in the NICU (21). Most studies have examined the cut-off values of hyperglycemia in NICU on children's age group (22-24, and 19), while our study's population were full-term newborns with the mean age of 5.5 days and mean birth weight of 2.52 kg who were candidates for the open abdominal surgery.

The mean of blood glucose which was obtained through four times post-surgery measurements was the assessment criteria in the present study. However, in other studies, the assessment criteria were the highest blood glucose levels during one or two times post-surgery measurements (19, 22). None of the infants in our study had blood glucose less than 40 mg/dl. Therefore, in previous studies, blood glucose>150 mg/dl was considered a cut-off for high blood glucose and blood glucose≥180 mg/dl as extremely high blood glucose requiring intervention (1, 19, 23, and 24). However, in the present study, the blood glucose of 40-179 mg/dl was regarded as relatively normal blood glucose and blood glucose≥180 mg/dl as hyperglycemia.

Our study group had approximately equal gender ratio (i.e., female=male) and 35.6% low birth weight. Ventilator dependency was observed in 46.7% of the patients. The mean blood glucose post-surgery in the selected population was 161.55 mg/dl. Moreover, in one-third of infants, the mean of post-operative blood glucose was≥180 mg/dl.

In line with the findings of the present study, several studies, such as Yang Wu et al. reported a high incidence of hyperglycemia in neonates undergoing abdominal surgery (25).

Perhaps some of these factors, including the way of initiating feeding, diet composition, trauma, tissue damage, and finally post-operative care can be directly related to the changes in blood glucose levels (8). Post-operative hyperglycemia has several consequences (e.g., increased risk of infection, delayed wound healing, ventilator dependence, length of stay, and mortality rate) (6, 26). Most studies have shown a high prevalence of hyperglycemia and the importance of monitoring blood glucose in these conditions (27-29). Pieces of evidence explained significant difference between pre- and early hour's post-operative blood glucose levels (28).

Hays et al. reported that a major cause of post-operative hyperglycemia is the effect of anesthetic injections and the release of catechol amines and cortisol (5).

According to the evidence, prolonged increase in blood glucose, lactate, pyruvate, and serum fatty acids during the first 12 h after the surgery may be due to the high rate of glycogenlysis, gluconeogenesis, and lipolysis in critical conditions (29).

It was observed that 87.5% of infants with low birth weight were hyperglycemic ($P<0.001$). Similar to this result, in a study conducted by G.Srinivasa et al., blood glucose level after the surgery was inversely associated with birth weight (28). Low birth weight is a primary risk factor in the development of hyperglycemia (4).

The novelty of the present study was in comparing the blood glucose during the first 24 h post-surgery with calorie and macronutrient intakes. Our results showed that calorie ($P=0.001$) and carbohydrate ($P<0.001$) intakes were higher in the hyperglycemic group than relatively normal glycemic group. In addition, it was observed that energy intake from fat sources was inversely related to increased blood glucose after the surgery. Fat intake was less in hyperglycemic infants than relatively normal glycemic infants ($P=0.04$). These results were similar when their intakes, were compared with optimal amount of calories and macronutrients after the surgery (4-8 mg/kg/min of carbohydrates, 2 gr/kg/day of protein, 1 gr/kg/day of fat, and energy to maintain 65 kcal/kg/day of weight) (13,16). As a result, calorie, carbohydrate, and protein intakes were in the optimal range in hyperglycemic group. In contrast, fat intake was approximately 1.5 times higher than optimal amounts for relatively normal glycemic infants.

Robert. W, et al. revealed that the energy requirement is reduced after the surgery in infants because of a halt in the growth progress. Excessive energy intake leads to more CO_2 and lipogenesis production. In the mentioned study, the mean of calorie intake after the operation was measured at 64.56±18.51 kcal/kg/day and in comparison with the amount needed by indirect calorimetry, it was observed that approximately 50% more calorie is prescribed than the predicted energy in hyperglycemic infants after the abdominal surgery (10). In critical condition after the surgery, infants need for energy does not increase and excessive calorie has undesirable impacts on clinical outcomes (30). In a study carried out by Nilesh et al., in comparison with indirect calorimetry in 83% of infants admitted to NICU, more than 8,000 kcal/week excessive energy was prescribed leading to an increase in the length of stay and ventilator dependency (31).

In our logistic regression model, carbohydrate intake was observed as an effective factor in the elevation of blood glucose; therefore, in the current study per each gram of carbohydrate in parenteral nutrition, the probability of high blood glucose≥180 mg/dl increased by 8%.

In a study conducted by M.O. Jones et al. different values of carbohydrate (10-25 gr/kg/day) were examined. Their observations showed that when glucose intake reached more than 18 gr/kg/day, the $\dot{V}O2$ (oxygen consumption), $\dot{V}CO2$ (carbon dioxide elimination), REE (Resting Energy Expenditure), and respiratory rate increased. In addition, respiratory quotient rose higher than 1 gr/kg/day. They concluded that when there is maximum glucose intake, pure oxidation of fat stops and endogen fat production begins. Moreover, the thermic effect of glucose increases and efficiency of body in metabolizing glucose reduces, leading to increased levels of blood glucose (32). Reduced glucose injection after the surgery safely prevents hyperglycemia in children (17). The initial dose of intravenous injection of glucose is an important risk factor in the development of hyperglycemia. Intravenous injection of glucose higher than 3-4 mg/kg/min after the surgery is associated with permanent hyperglycemia (27).

The comparison of the mean blood glucose levels in the two groups based on receiving fat emulsion through parenteral nutrition showed that per each gram of fat intake, the possibility of blood glucose levels≥180 mg/dl reduced to 7%. Effects of fat emulsion intake on blood glucose after the surgery was evaluated in different studies; however, discrepancies were observed in several studies. In some studies, the administration of fat emulsions through parenteral nutrition has been reported as a reason for increase in blood glucose as much as 24% more than the normal values (17, 33).

At the time of adding glucose and amino acids to intravenous fat emulsions, the fat leads to an increase in blood glucose. Fat suppresses the effect of the liver on insulin secretion and leads to increased peripheral insulin resistance (17, 33).

Agostino .P, et al. showed that after the abdominal surgery, the major determinant of fat consumption is carbohydrate intake and basal energy level. Improved fat intake by reducing the ratio of carbohydrates to fat in intravenous nutrition reduces the activity of free radicals (13).

John.B. D et al. reported that the high proportion of carbohydrate/fat (too much carbohydrates intake) during intravenous injection may cause a turnover of enzymes involved in fat and lipogenesis metabolism (34).

In the present study, protein intake during parenteral nutrition had no significant difference between the two groups of blood glucose. Given that no significant difference was observed between the two groups of blood glucose in protein intake from the percentage of optimal values.

Protein intake is more important in infants than adults. Referring to the results in a study conducted by Agostino P, et al., it shows that protein metabolism in infants undergoing surgery is different from adults due to surgical trauma and infection. Moreover, protein turnover is faster and a tendency to maintain nitrogen is higher in infants (33). In addition, protein intake can be influenced by other dietary compositions. Low-calorie parenteral diet and use of fat emulsions increase the proportion of protein in anabolism and prevent elevation in blood glucose levels after the surgery (13).

Limitations

Limitations of the present study include the followings which if fixed, more complete results may be achieved:

1. If a larger sample size is selected, the results of such studies can reveal the role of factors affecting treatment outcome (e.g., age and ventilation dependency) more significantly.
2. Measured samples for blood glucose after the surgery were complete. Blood glucose was measured every 6 h for 24 h after the surgery using a glucometer. It was evident that complete blood glucose samples were affected by hematocrit and error of glucometer and usually the values obtained from them showed a 10-15% difference than the actual amounts (35, 36). Given that blood serum sample collection requires more blood samples from newborns and is influenced by stress of the surgery, a glucometer was used to measure the samples.

3. Blood glucose 6 h after the surgery was not considered in the calculation of the mean blood glucose. The surgery was performed on most infants in a short time post-admission to NICU; therefore, using blood glucose values before the surgery was not possible.
4. Regarding the retrospective nature of the present study, there were many therapeutic measurements between two sampling times, which can disrupt the blood glucose level. These factors should be considered in further researches.
5. The energy levels of serum glucose during the surgery, type of post-operative intravenous sugar solution, and also the speed of fat emulsion injection or intravenous dextrose after the surgery were not considered in the current study. Given that these factors may have an impact on blood glucose levels, it is recommended to consider their effect on blood glucose after the surgery in future studies.

Conclusion

The present study was noteworthy because it was the first study that evaluated blood glucose levels with measuring energy and macronutrient intakes in full-term neonates after the open abdominal surgery. Based on findings of the current research, hyperglycemia after the surgery was related to birth weight. In addition, it was observed that the use of extra calories was not beneficial for the infants after the surgery, because their basic metabolic energy does not increase after the surgery (except for 3-4 h after the surgery). The energy supply after stable condition of post-operative infants is considered based on response to growth and stress.

The amount of glucose injection during parenteral nutrition was discovered to be an important factor in the development of high blood glucose after the surgery. Furthermore, the proper administration of fat emulsion solution regarding the decrease in the ratio of carbohydrate to fat can decrease blood glucose after the surgery. In addition, proper administration of fat emulsion can reinforce the effect of dietary protein in the improvement of the anabolism after the surgery.

Conflicts of interests

None.

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