

Original

Study of hyperglycemia in non critically-ill patients receiving parenteral nutrition; incidence and risk factors

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Abstract

Background: The objectives of our study on non-critically ill patients receiving parenteral nutrition (PN) are to assess the incidence of hyperglycemia, the risk factors associated to its development and its influence in patient's evolution.

Methods: A multicentric prospective observational study was performed in 9 hospitals. Four multivariate studies were developed to study the temporal risk in the occurrence of hyperglycemia (endpoint), intensive care unit (ICU) admission, length of stay (LOS) and death. Demographics, nutrients, drugs and clinical variables were collected. Independent variables studied as a possible risk factors were: sex, diabetes mellitus 2, baseline glycemia, albuminemia, pancreatitis, surgery in the 7 days prior to the end point, infection, insulin/somatostatin/corticoids administration during the study, glomerular filtration rate (GFR), and difference in the amount of glucose administration between the endpoint and one day before.

Results: 119 patients were enrolled in the study, 25 cases of hyperglycemia were detected. In the clinical factors associated with PN hyperglycemia, significant variables were: surgery in the 7 days before the end point, GFR, glucose load in the 24 hours previous to the end point insulin administration and somatostatin/octreotide administration during the study. Hyperglycemia was significantly associated with ICU admission and increased LOS.

Conclusions: Glucose administration in non-critically ill patients receiving PN should be reassessed downwards, especially in the immediate postsurgery, renal impairment and in patients treated with somatostatin analogues. It should be taken into account that an increase in glucose dose may lead to hyperglycemia in these patients and hyperglycemia correlates with longer hospital stay and increased frequency of ICU admissions.

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Key words: Parenteral nutrition. Hyperglycemia. Not-critically ill patients. Hyperglycemia risk factors.

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ESTUDIO DE HIPERGLICEMIA EN PACIENTES NO CRÍTICOS TRATADOS CON NUTRICIÓN PARENTERAL; INCIDENCIA Y FACTORES DE RIESGO

Resumen

Antecedentes y objetivo: El estudio está dirigido a pacientes no críticos tratados con nutrición parenteral (NP) y tiene como objetivo evaluar la incidencia de hiperglucemia, los factores de riesgo asociados a su aparición y su influencia sobre su evolución clínica.

Métodos: Estudio multicéntrico prospectivo y observacional en 9 hospitales. Se construyeron 4 modelos multivariantes para estudiar el riesgo de aparición de hiperglucemia (evento final), el ingreso en cuidados intensivos (UCI), el tiempo de hospitalización y muerte. Se recogieron variables demográficas, de nutrientes aportados, medicación y variables clínicas. La variables independientes estudiadas como posibles factores de riesgo fueron: sexo, diabetes mellitus tipo 2, glucemia basal, pancreatitis, cirugía en los 7 días previos al evento final, administración durante el estudio de insulina/somatostatina/corticoides, nivel de filtración glomerular (GFR) y las diferencias entre el aporte de glucosa administrada entre el evento final y el día previo.

Resultados: Se incluyeron 119 pacientes, de los cuales 25 presentaron hiperglucemia. Entre los factores clínicos asociados a la aparición de hiperglucemia, las variables significativas fueron: la cirugía en los 7 días previos al evento final, GFR, carga de glucosa en las 24 horas previas al evento final, administración de insulina y de somatostatina/octreotido. La hiperglucemia se asoció significativamente al ingreso en UCI y a la estancia hospitalaria.

Conclusión: La administración de glucosa en pacientes no críticos en tratamiento con NP debería ser reevaluada con criterios restrictivos, especialmente en el postoperatorio inmediato, en insuficiencia renal y en pacientes tratados con análogos de la somatostatina. Debería tenerse en cuenta que los incrementos del aporte de glucosa se asocian a hiperglucemia, y esta se correlaciona con un incremento de la estancia hospitalaria y a una mayor frecuencia de ingresos en UCI.

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Palabras clave: Nutrición parenteral. Hiperglucemia. Pacientes no críticos. Factores de riesgo asociados a hiperglucemia.

Introduction

Hyperglycemia during hospitalization has been linked to a poor outcome in patients without previous diagnose of diabetes.^{1,2} Stress hyperglycemia and its control in critically ill patients have generated a great number of studies in the recent past.^{3,4,5,6} Hyperglycemia has also been associated to worse illness markers, increased morbidity, or mortality in non-critically ill patients suffering coronary artery disease, stroke, pneumonia, undergoing surgical procedures, and in organ transplantation.^{1,2} Hyperglycemia is the most common complication in patients on parenteral nutrition (PN) since they receive great amounts of glucose as part of their nutritional support.⁷ Hyperglycemia during PN has also been associated to increased complication rate and mortality. In recent studies, increased blood glucose during PN resulted in increased risk of cardiac complications, infection, systemic sepsis, acute renal failure, respiratory failure, and death.^{8,9,10,11,12} The prevalence of hyperglycemia during PN has been scarcely studied in recent years, when caloric requirements have decreased compared to former guidelines and strict glycemic control has been implemented.¹³ Hyperglycemia has been reported on 17% to 44% of patients under PN.^{9,11,12,14} Glucose load has been considered the main factor for developing hyperglycemia during PN and other factors are also known to predispose to this complication,^{7,14} but their importance varies in function of the clinical features of patients.

Most of studies of hyperglycemia in PN refer to critically ill patients due to their hypermetabolic state leading to a difficult control of glucose levels. However, there are few studies in non-critically ill patients with gastrointestinal tract impairment and hence, candidates for PN. These type of patients are in principle expected to have a better tolerance to glucose load.

The objectives of our study on non-critically ill patients receiving PN are to assess the incidence of hyperglycemia, the risk factors associated to its development and its influence in patient's evolution.

Material and methods

Study design and study population

A multicentric prospective observational study was performed from July 2007 to August 2008 in 9 different hospitals. Patients older than 18 years on treatment with total PN as their only energy supply were included. Exclusion criteria were diabetes mellitus type I, diabetes mellitus type II requiring insulin treatment, patients with glycemia ≥ 180 mg/dL (≥ 10 mmol/L) 24 hours prior to PN or admission in Intensive Care Unit (ICU) before starting PN.

Patients were followed until the endpoint was achieved. This was defined as: a documented event of

hyperglycemia (glycemia ≥ 180 mg/dL or ≥ 10 mmol/L, measured either by capillary or plasma glycemic level), end of the PN or establishment of enteral/oral feeding (except for water).

Data collection

Information was collected:

- Demographics: sex, age and body mass index (BMI) calculated by the formula: $\text{weight (kg)/[height (m)]}^2$.
- Clinical variables:
 - Past medical history as: non-insulin-dependent type II diabetes, dyslipidemia, chronic renal impairment and/or hypertension.
 - PN indication.
 - Pancreatitis [yes/no].
 - Surgery [yes/no] and days between surgery and the endpoint.
 - Infection: the type of infection was classified as wound infection, sepsis or other infections. Based on the ACCP/SCCM consensus conference,¹⁵ sepsis was established when the patient presented systemic inflammatory response syndrome (SIRS) due to infection. SIRS was confirmed by at least two of the following criteria: (a) fever $\geq 38^\circ\text{C}$ or $\leq 36^\circ\text{C}$, (b) tachycardia with heart rate ≥ 90 beats/min, (c) tachypnea with $\text{pCO}_2 \leq 32$ mmHg or mechanical ventilation; (d) leukocytes $> 12 \times 10^9$ cells/L. If the patient additionally met the criteria for associated persistent hypotension despite adequate fluid resuscitation or the necessity of vasopressor administration to maintain a mean arterial blood pressure of 70 mmHg, the case was classified as septic shock.
 - ICU admission after the endpoint [yes/no].
 - Hospital length stay [days].
 - Death [yes/no].
- Nutrients and drugs:
 - Glucose, lipids and nitrogen administered at the endpoint [g/kg/day].
 - Glucose administered in the 24 h prior to the endpoint both in the PN and in dextrose solutions [g/kg/day] and the difference in the amount of glucose administration between the final event day and 24 h prior.
 - Duration of PN treatment expressed in days until the endpoint.
 - Insulin administration during the study [yes/no].
 - Administration in the 48 h before the endpoint of somatostatin/octreotide and/or corticoids [yes/no].
- Plasma samples were collected daily at 7 am and those obtained at the endpoint (and if not available, those obtained the day before or after) were

Table I
Baseline characteristics (value and % or mean \pm SD)

Characteristics	All N = 119	Hyperglycemia		p value
		Yes N = 25 (21.0%)	No N = 94 (79.0)	
<i>Demographics</i>				
Male (%)	70 (58.8)	11 (44.0)	59 (62.1)	0.09
Age (y)	61.5 \pm 18.1	66.8 \pm 13.3	60.1 \pm 18.9	0.05
BMI (kg/m ²)	24.3 \pm 5.2	24.8 \pm 6.1	24.2 \pm 4.9	0.66
<i>Clinical variables</i>				
Type 2 diabetes (%)	3 (2.5)	1 (4.0)	2 (2.1)	0.50
Dyslipemia (%)	16 (13.4)	4 (16.0)	12 (12.8)	0.74
Chronic Renal Impairment (%)	3 (2.5)	2 (8.0)	1 (1.1)	0.11
Hypertension (%)	39 (32.8)	12 (48.0)	27 (28.7)	0.07
<i>PN indication (%)</i>				
Postoperative ileus	20 (16.8)	2 (8.0)	18 (19.1)	
Postoperative complications	43 (36.1)	13 (52.0)	30 (31.9)	
Bowel rest	31 (26.1)	6 (24.0)	25 (26.6)	
Occlusion	13 (10.9)	3 (12.0)	10 (10.6)	
Others	12 (10.1)	1 (4.0)	11 (11.7)	
Pancreatitis (%)	17 (14.3)	5 (20.1)	12 (12.8)	0.36
Surgery (%)	78 (65.5)	18 (72.0)	60 (63.8)	0.44
Glycemia, baseline (mg/dL)	99.5 \pm 15.9	102.6 \pm 18.7	98.7 \pm 15.2	0.34
Creatinine (baseline) (mmol/L)	74.07 \pm 59.1	99.0 \pm 120.2	67.4 \pm 22.7	0.20

included in the study. Plasma determinations were:

- Glucose blood levels [mg/dL] and hyperglycemia (> 180 mg/dL)
- Renal function measured as plasmatic creatinine and calculated glomerular filtration (MDRD-4). Renal function impairment was defined as GFR < 60 mL/min/1,73m².
- Albumin [g/L].

All data were collected in each hospital using their own record information and blood analysis systems, and put together in a single database for the analysis.

Statistical analysis

To study the risk factors related with hyperglycemias, univariate and multivariate statistics analyses were performed using IBM Statistics SPSS 19.

The univariate tests used were Chi-square for categorical variables and t-test for quantitative variables. These tests were performed to search for statistical differences in the variables between patients that developed hyperglycemia and those who did not.

Four multivariate studies were performed: one Cox proportional hazards regression model to study the temporal risk of the hyperglycemia occurrence (endpoint), two logistic regressions for the dependent variables of death and ICU admission; and one multiple linear regression for the dependent variable of

hospital length stay. All variables were included by a stepwise method ($p < 0.1$ for inclusion). Significance was studied using the confidence interval.

In the Cox regression model to determine the clinical factors associated with hyperglycemia occurrence, independent variables studied as a possible risk factors were: sex, diabetes mellitus type 2, pancreatitis, surgery in the 7 days prior to the endpoint, infection, difference in the amount of glucose administration between the endpoint and the day before; insulin, somatostatin and corticoids administration during the study; baseline glycemia, GFR and albumin blood level.

To determine the clinical factors associated with ICU admission, hospital length stay and death, the independent variables studied as possible risk factors were: diabetes mellitus type 2, surgery, infection, hyperglycemia, GFR and albumin blood levels.

Results

A total of 119 patients were enrolled in the study. For 96.6% of patients at least one daily determination of glucose was performed. Hyperglycemia (> 180 mg/dL) was detected in 25 cases (21%) after an average of 4.2 ± 3.6 days after starting PN. The group of patients without hyperglycemia received PN for a period of 9.3 ± 6.6 days. There were no differences in the baseline characteristics between the group that developed hyperglycemia and the rest of patients studied except for age (table I). Eight determinations of

Table II
Concurrent conditions during the study period and nutrients administered

Variables	All	Hyperglycemia		p value
		Yes	No	
Glucose total at the endpoint (g/ kg/day)	3.0 ± 0.9	3.0 ± 1.0	3.0 ± 0.9	0.96
Lipids at the endpoint (g/ kg/day)	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.3	0.75
Proteins at the endpoint (g/kg/day)	1.18 ± 0.37	1.13 ± 0.25	1.18 ± 0.37	0.60
Glucose total (day -1) ¹ (g/kg/day)	3.0 ± 1.0	2.9 ± 1.1	3.1 ± 0.9	0.48
Glucose (variation) ² (g/kg/day)	-0.03 ± 0.86	+0.11 ± 0.60	-0.1 ± 0.24	0.14
Insulin use ³ (%)	19 (15.9)	10 (40.0)	9 (9.6)	<0.01
Somatostatine/Octreotide use (%)	14 (11.8)	6 (24.0)	8 (8.5)	0.08
Corticosteroids use (%)	19 (15.9)	3 (12.0)	16 (17.0)	0.78
Glycemia, end point (mg/dL)	129.18 ± 41.59	199.18 ± 20.19	110.48 ± 20.20	<0.001
Glomerular filtration rate ⁴ (mL/min/1.73 m ²)	107.63 ± 57.6	95.84 ± 56.1	110.7 ± 47.2	0.19
Albumin (g/L)	28.5 ± 6.3	27.8 ± 7.7	28.7 ± 5.9	0.61
Infection (all) (%)	40 (32.8)	10 (41.7)	30 (30.6)	0.34
Wound infection	19 (15.9)	5 (20.8)	14 (14.9)	0.72
Sepsis	7 (5.9)	2 (8.0)	5 (5.3)	0.45
Others focus	14 (11.8)	3 (12.0)	11 (11.2)	0.45
ICU admission (%)	6 (5.0)	5 (20.0)	1 (1.1)	<0.01
Length of stay (days)	31.21 ± 23.8	41.68 ± 28.0	28.43 ± 21.7	<0.01
Death (%)	9 (7.6)	4 (16.0)	5 (5.3)	0.09

¹Total glucose administered 24 h prior final event.

²Difference in the amount of glucose administration between the final event day and 24 h prior.

³Insulin administration during the study.

⁴Glomerular filtration rate calculated by MDRD 4.

plasma glucose out of a total of 362 (2.2%) were lower than 50 mg/dL and were corrected by adjusting the pattern of insulin.

Table II shows clinical variables during the study period in both groups and the amount of nutrients administered. The group of patients with hyperglycemia had significantly more days of stay and more ICU admissions than the group without hyperglycemia. The mean amount of glucose, lipid and proteins administered in the 24 h prior to the endpoint were 3 ± 0.9 g/kg/day, 0.7 ± 0.4 g/kg/day and 1.2 ± 0.4 g/kg/day, respectively.

The significant variables, as yielded by the statistical model constructed to determine the clinical factors

associated with hyperglycemia, are summarized in table III. Significant variables were: surgery in the 7 days before the endpoint, glomerular filtration rate, the difference of glucose amount administration in the 24 h previous to the endpoint. insulin administration and somatostatine/octreotide administration.

The only variable studied associated with a risk of ICU admission was having a hyperglycemic episode OR = 23.2 [IC 95%: 2.57-209.98]. The hospital length of stay significantly increased with high values of glycemia at the endpoint coefficient b = 0.19 [IC 95%: 0.01-0.219] and showed a tendency with the presence of infection coefficient b = 0.17 [IC 95%: 0.05-17.55]. In the death model none of the variables was significant.

Table III
Estimated Odds Ratios from Cox proportional hazards regression model to determine clinical factor associated with hyperglycemia

Variables	Odds ratio	Confidence interval 95%	p value
Surgery ≤ 7 days	5.65	2.27-14.07	<0.001
Glomerular filtration rate ¹	0.99	0.98-0.99	0.045
Glucose (variation day-1) ² (g/kg)	5.73	2.04-16.07	<0.001
Insulin administration ³	3.60	1.53-8.48	0.003
Somatostatine/Octreotide administration	3.20	1.16-8.83	0.025

¹Glomerular filtration rate calculated by MDRD 4.

²Difference in the amount of glucose administration between the final event day and 24 h prior.

³Insulin administration during the study.

Discussion

In our prospective series of non-critically patients treated with PN, we found that hyperglycemia was present in 21% of the patients, meaning that approximately one in every five patients treated with PN presented hyperglycemia. This complication was found to be related to surgical procedures in the previous 7 days, the use of somatostatin or octreotide, impaired renal function and the increase of glucose infused in the 24 h previous to the endpoint. In addition, those patients who developed hyperglycemia were more frequently admitted to ICU and had a longer hospital stay

Although similar studies showed lower rates of hyperglycemia, they were made with higher cut-offs for hyperglycemia.^{16,17} Therefore, it is reasonable to assume that they could have higher rates with our thresholding. In fact, our incidence of hyperglycemia agrees with a recent study in non-critically ill patients with PN⁹ that showed an incidence of 17% with a cut-off of 180 mg/L (10 mmol/L). Our results are in accordance with these in previous studies showing that patients with higher blood glucose levels during PN have longer hospital stay and more ICU admissions.^{8,10,11} In contrast, no relationship was found between hyperglycemia and in-hospital mortality as prior works did.^{8,9,10,11} This situation together with the lack of relationship between infection/sepsis and hyperglycemia may be due to the less critically ill population studied in comparison to other studies, which included both critically and non-critically ill patients.

Several investigators have reported hyperglycemia as a complication of PN use; however, several changes in clinical practice have been occurring in the last years proposing low levels for the standard control of glycemia. It has been shown that maintaining normoglycemia improves outcome, but may result in hypoglycemia¹⁸ and associated metabolic disturbance. In our series, given the profile of patients, the onset of hypoglycemia was irrelevant.

On the other hand, poor glycemic control is a particular problem in post-operative patients receiving PN and is associated with poorer outcome and increased septic complications. Surgery, like other aggressions, lead to a chain reaction including release of stress hormones and inflammation mediators like cytokines, with a high impact on the metabolic situation in order to achieve a correct wound cicatrization.¹⁹ In this context, we found that during recent post-surgery period (≤ 7 days) patients treated with PN had significant more incidence of hyperglycemia independently of the amount of glucose intake. One way to control glycemia level has been proposed by Lidder et al.²⁰ who showed that, in a specific postoperative situation (postoesophagectomy). Glycemic control can be improved by a regimen that combines enteral with parenteral feeding. Nevertheless, in our study, patients

that could tolerate some oral or enteral nutrition were excluded.

Gluconeogenesis and reabsorption of filtered glucose are the main kidney mechanisms affecting glucose homeostasis together with insulin metabolism.²¹ In patients with kidney injury, hyperglycemia and insulin resistance are common findings.²² In addition, uraemia has been associated to decreased glucose tissue uptake.²³ In our study, we found that patients with impaired renal function have more incidence of hyperglycemia.

Current guidelines for PN recommend glucose infusions of no more than 5-7 mg/kg/min because stress-induced hypercatabolism reduces the ability to oxidize glucose and potentially induces lipogenesis, fatty liver, and hyperglycemia.^{24,25} A recent study reported a glucose administration rate over 4 mg/kg/min as the only predictor of hyperglycemia in surgical patients.²⁶ Glucose and caloric infusions for our cohort were consistent with current nutrition support practice guidelines (mean glucose 2.08 mg/kg/min; 23.7 kcal/kg), and none of our participants received more than 4 mg/kg/min. However, we found that a rise in glucose load within the last 24 hours is related with hyperglycemia. In fact, the risk of hyperglycemia increased 5.73 times (CI 95%: 2.1-16.1) per each extra g/kg/day administered in comparison with the day before of the hyperglycemia development.

Since hyperglycemia occurring during PN treatment is associated with increased adverse outcomes and mortality in patients receiving PN;^{10,11} staff involved in nutrition support should be aware that patients on PN after recent surgery and renal impairment have more probability of developing hyperglycemia. The current literature documenting the adverse effects of hyperglycemia prompts a need to identify patients at risk and the development of guidelines that ensure that PN administration does not precipitate hyperglycemia. Prophylactic use of insulin in PN may be considered when administered to risk patients for whom an increase in glucose load is planned. Our results agree with studies published^{27,28} in which patients who needed insulin to control their glucose homeostasis presented an increased risk of hyperglycemia.

Therapy with somatostatin analogues affects glucose homeostasis by inhibiting insulin pancreatic secretion. Nevertheless, even when administered under conventional dosing regimens the clinical impact is marginal, it could be sufficient to trigger a hyperglycemic event.^{29,30} Our results are in accordance with those in previous studies where patients treated with somatostatin analogues showed high risk to developing hyperglycemia.

This study has some limitations. First, it does not evaluate the effects of persistent hyperglycemia, because hyperglycemia has been defined as a single episode appearance. In addition, patients have been collected in several hospitals with different protocols for monitoring blood glucose; therefore, there was not

a unique protocol to control hyperglycemia and euglycemia for all patients included.

In conclusion, our results suggest that in addition to most of the current guidelines considerations, glucose parenteral load in non-critically ill patients receiving PN should be reassessed downwards, especially in the immediate postsurgery, renal impairment and in patients treated with somatostatin analogues. It should be taken into account that an increase in glucose dose may lead to hyperglycemia in these patients and hyperglycemia correlates with longer hospital stay and increased frequency of ICU admissions.

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