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BRIEF REPORT

Differences in Glycemic Control in Diabetic and Non-diabetic Patients with Parenteral Nutrition Using a Basal plus Correction Insulin Regimen: An Observational, Retrospective Study

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ABSTRACT

Introduction: Hyperglycemia is a frequent complication of parenteral nutrition (PN) in patients both with and without diabetes mellitis (DM). The aim of this study was to evaluate the quality of glucose control achieved with basal plus-correction insulin in surgical patients with and without a history of DM receiving PN.

Methods: Retrospective evaluation of a protocol applied during the period of January 2013–December 2015. The insulin dose was started at 0.4 and 0.3 IU/kg/day in patients with previous DM and without a history of DM, respectively, and the target blood glucose (BG) was < 180 mg/dl. Mean BG levels, insulin total daily dose (TDD) and hypoglycemic (< 70 mg/dl) events on different days of PN were also evaluated.

Results: Forty-one patients with previous type 2 DM and 39 without DM were evaluated. Glycemic control in both groups was as follows: during the first 48 h (230.4 ± 67 vs. 189.4 ± 38 mg/dl, $p = 0.002$); at the midpoint (224.6 ± 58 vs. 181.3 ± 27 mg/dl, $p = 0.003$); 48 h before ending TPN (196.4 ± 43 vs. 169.8 ± 40 mg/dl, $p = 0.004$). Insulin TDD was 0.5 ± 0.3 U/kg/day in patients with DM and 0.37 ± 0.3 units/kg/day in those without DM ($p < 0.05$). A total of 18 patients experienced hypoglycemic events, without differences between the groups.

Conclusion: A basal-correction insulin regimen is an alternative method for managing hyperglycemia in non-critically ill surgical patients on PN.

Keywords: Diabetic patients; Hyperglycemia; Non-diabetic patients; Parenteral nutrition

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INTRODUCTION

Hyperglycemia is an important side effect in patients receiving parenteral nutrition [1] because of its high prevalence and has been associated with adverse outcomes [2].

The prevalence of hyperglycemia in patients receiving PN is high and reported in more than 40% of these patients [3–5]. Most studies refer to critically ill patients because their hypermetabolic state makes controlling glucose levels difficult, and there are few studies of non-critically ill patients, who are expected to have a better tolerance of the glucose load. PN-related hyperglycemia is associated with poor clinical outcomes in patients with and without DM as well as those who are either critically or non-critically ill [6–9]. In surgical patients, hyperglycemia increases risks of perioperative complications, length of stay and mortality [10, 11].

Both the consensus statement by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) as well the clinical practice guideline of the Endocrine Society recommend a premeal BG level < 140 mg/dl and random BG values < 180 mg/dl [12, 13]. Furthermore, the American Society for Parenteral and Enteral Nutrition recommends a blood glucose goal of 140–180 mg/dl for hospitalized patients receiving nutritional support [14].

Insulin is the treatment of choice to control hyperglycemia during PN. Subcutaneous insulin administration, intravenous insulin infusion and addition of insulin to the PN bag have been shown to be effective in managing hyperglycemia in these patients [5, 13, 15, 16]. However, there are few data from clinical trials comparing different strategies [17], particularly in non-critically ill patients [18, 19]. Furthermore, insulin protocols vary widely between institutions.

In our hospital, a program for hyperglycemia management based on a published protocol was established [20]. For non-critically ill patients under continuous PN, a basal plus correction insulin regimen was set up. The aim of this study was to evaluate the quality of glucose control achieved by this strategy in surgical patients with and without a history of DM receiving PN.

METHODS

A retrospective study of surgical patients receiving PN during the period of January 2013–December 2015 was performed at the Hospital de la Santa Creu i Sant Pau in Barcelona, Spain. Data were retrieved from the hospital's electronic medical records. Patients with or without a previous history of DM treated with a basal plus correction insulin regimen were included. In the diabetic patient group, those with no record of DM but a glycated hemoglobin (HbA1c) measurement ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dl were also included. Patients were excluded if they were transfered to intensive care units (ICUs), the duration of the PN was < 5 days or > 60 days, or they had recieved pharmacologic doses of corticosteroids. The study was approved by the Ethics Committee of our institution, the Hospital de la Santa Creu i Sant Pau.

Parenteral Nutrition Administration

The TPN formula was provided as a total nutrient admixture solution containing carbohydrates, proteins and lipids, with daily adjustments according to the individual caloric and nutritional requirements of the patients. PN administration provides approximately 50–60% of the calculated daily carbohydrate caloric requirements during the first 24 h and was increased to the desired goal during the next 24 h. The glucose range administered was between 150 and 250 g.

Blood Glucose Monitoring and Insulin Therapy Protocol

In all patients receiving PN, capillary BG was monitored every 6 h and was discontinued in patients without a prior history of DM if glucose values were < 140 mg/dl without insulin therapy for 48 h with the desired caloric intake.

Insulin therapy was indicated for all patients with previous DM under pharmacologic therapy. In DM patients treated exclusively with a diet and in those without a history of DM, insulin therapy was indicated if blood glucose levels were > 180 mg/dl. Patients with previous replacement insulin therapy with a basal-bolus regimen or ≥ two doses of intermediate-acting or premixed insulin were started at their

previous total daily dose (TDD), and in the remaining patients the initial TDD was estimated as 0.4 U/kg/day.

The TDD was administered as basal insulin glargine once daily, and correction doses of insulin lispro were administered every 6 h if glycemia remained above 180 mg/dl. The glargine insulin dose was increased or decreased by 10–20% every day to achieve a glycemic goal of 140–180 mg/dl.

The glycated hemoglobin (HbA1c) was determined in all patients with previous diabetes and in non-diabetic patients who required insulin therapy.

Outcome Measures

The primary outcome of this study was to determine the quality of glycemic control as measured by mean daily BG levels 48 h after initiation of PN treatment, at the midpoint of the treatment period and 48 h before ending PN. The number of hypoglycemic (< 70 mg/dl) events and TDD of insulin were also determined, and information on the demographics, DM characteristics, type of surgery, BG on admission and hospital length of stay (LOS) were collected.

Statistical Analysis

All statistical analyses were performed with the STATA 13 statistical program.

A p value < 0.05 was set as statistically significant.

Descriptive statistics using frequencies to summarize categorical variables (percentage) and expressing quantitative variables as mean ± standard deviation (SD) were performed. Normal distribution of quantitative data was assessed using the Shapiro-Wilk test.

The univariate tests used were chi-square for categorical variables and Student's t-test for quantitative variables. Paired Student's tests were performed to search for statistical differences in the variables between DM and non-DM patients.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

The baseline characteristics of the 80 patients who met the eligibility criteria are shown in Table 1. There were no significant differences in age, body mass index, weight, mean LOS, type of surgery or mean duration of PN between DM and non-DM patients. The most common reason for indicating PN was a paralytic ileus. Patients with a prior history of DM had significantly higher admission BG and HbA1c values (Table 2).

Glycemic Control

Mean daily BG concentrations during the hospital stay are shown in Fig. 1.

In all patients the mean BG levels during the first 48 h of PN, at the midpoint period of PN and 48 h before ending PN were 209.9 ± 58, 201.1 ± 43 and 183.1 ± 44 mg/dl, respectively. Patients with previous DM had higher mean BG concentrations at the three study times (Fig. 1). There were no differences between DM patients with or without previous insulin therapy during the first 48 h of PN (230.5 ± 67 vs. 221.6 ± 70 mg/dl), at the midpoint of the period with PN (221.8 ± 58 vs. 233.0 ± 60 mg/dl) and 48 h before ending PN (196.4 ± 43 vs. 193.92 ± 43 mg/dl), $p > 0.05$. The proportion of patients who achieved BG < 180 mg/dl is shown in Fig. 2.

Eighteen (22.5%) patients experienced mild hypoglycemic events and six (7.5%) severe hypoglycemic events, with no differences between patients with or without previous DM.

Table 1 Clinical characteristics of the study patients (n = 80)

Variables	All patients (n = 80)	Diabetic patients (n = 41)	Non-diabetic patients (n = 39)	p value*
Age (years)	77.6 ± 9.1	77.6 ± 9.1	74.3 ± 10.4	0.07
Gender				0.27
Male, n (%)	50 (62.5)	28 (68.3)	22 (56.4)	
Female, n (%)	30 (37.5)	13 (31.7)	17 (43.6)	
BMI (kg/m^2)	27.3 ± 4.8	26.8 ± 5.2	27.8 ± 4.4	0.16
Body weight (kg)	73.5 ± 14.2	74.8 ± 13.5	72.1 ± 14.9	0.19
HbA1c (%)	6.8 ± 1.1	7.1 ± 1.1	6.2 ± 0.9	0.003
Previous diabetes treatment				
Diet, n (%)	–	9 (22)	–	–
Oral agents, n (%)	–	19 (46)		
Basal insulin + oral agents, n (%)	–	4 (10)	–	–
Basal insulin, n (%)	–	7 (17)	–	–
Basal–bolus insulin, n (%)	–	2 (5)	–	–
Type of surgery				0.43
Non-neoplasia surgery, n (%)	24 (30)	14 (34.2)	10 (25.6)	
Colorectal cancer, n (%)	19 (23.8)	11 (26.8)	8 (20.5)	
Pancreatic cancer, n (%)	18 (22.5)	6 (14.6)	12 (30.8)	
Other cancer	14 (17.5)	6 (14.6)	8 (20.5)	
Vascular surgery, n (%)	2 (2.5)	2 (4.9)	–	
Gynecologic cancer, n (%)	3 (3.7)	2 (4.9)	1 (2.6)	
TPN indication				0.09
Ileus	73 (91.3)	40 (97.6)	33 (84.6)	
Fistula	3 (3.7)	–	3 (7.7)	
Wound breakdown	4 (5)	1 (2.4)	3 (7.7)	
Duration of PN (days)	12 ± 8	13.2 ± 8.5	10.9 ± 7.6	0.89
Length of hospital stay (days)	30.7 ± 14.5	30.8 ± 14.3	30.7 ± 14.9	0.52

Data are mean ± standard deviation

*Difference between diabetic and non-diabetic patients

Table 2 Difference in glycemic control, hypoglycemic events and insulin treatment (n = 80)

Variables	All patients (n = 80)	Diabetic patients (n = 41)	Non-diabetic patients (n = 39)	p value*
Mean BG at admission (mg/dl)	165.9 ± 63	180.7 ± 66	146.3 ± 57	0.015
Total mean insulin dose, U/day	30.2 ± 20	35.1 ± 21	25.3 ± 19	0.02
Total mean insulin dose, U/kg/day	0.43 ± 0.3	0.50 ± 0.3	0.37 ± 0.2	0.05
48 h after start of PN				
Mean BG (mg/dl)	209.9 ± 58	230.5 ± 67	189.4 ± 38	0.002
Glargina insulin, U/day	11.5 ± 19	14.3 ± 20	8.5 ± 18	0.11
Lispro insulin, U/day	13.5 ± 20	16.9 ± 13	9.9 ± 8	0.007
Midpoint period of PN				
Mean BG (mg/dl)	201.1 ± 43	221.8 ± 58	180.1 ± 17	0.003
Glargina insulin, U/day	21.0 ± 26	26.0 ± 31	15.6 ± 18	0.03
Lispro insulin, U/day	15.4 ± 9	16.7 ± 11	14.0 ± 7	0.12
48 h before ending PN				
Mean BG (mg/dl)	183.1 ± 44	196.4 ± 43	169.8 ± 40	0.004
Glargina insulin, U/day	28.2 ± 28	28.2 ± 28	15.6 ± 18	0.02
Lispro insulin, U/day	13.3 ± 9	13.3 ± 9	7.8 ± 6	0.001
Hypoglycemic events				
BG < 70 mg/dl, n (%)	9 (22)	9 (22)	9 (23)	0.53
BG < 40 mg/dl, n (%)	2 (5)	2 (5)	4 (10)	

Data are mean ± standard deviation
BG blood glucose
*Difference between diabetic and non-diabetic patients

Most hypoglycemic episodes were due to unplanned discontinuation of PN.

Insulin Dose

Insulin requirements are shown in Table 2. The TDD of insulin during PN was 30.2 ± 20 units or 0.43 ± 0.3 U/kg/day. In patients with DM, the TDD was 0.5 ± 0.3 U/kg/day (35.1 ± 21 U/day) and, in those with no history of DM, 0.37 ± 0.3 U/kg/day (25.3 ± 19 U/day), $p < 0.05$. The insulin glargine dose increased while the correctional insulin lispro decreased from the start until 48 h before ending the PN.

Newly Diabetic Patients

We identified five newly diabetic patients, and the mean HbA1c was 7.2% ± 0.6%. At discharge, three patients received basal insulin and two oral agents.

DISCUSSION

This retrospective study aimed to evaluate the quality of glucose control achieved by a basal plus correction insulin regimen in surgical patients with and without a history of DM receiving PN. Our study confirms that

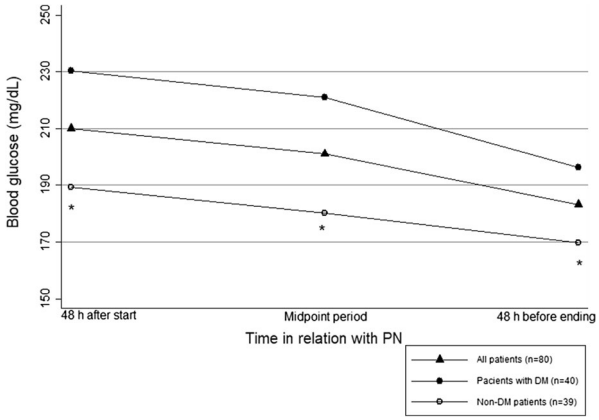

Fig. 1 Glycemic control in all patients, diabetic and non-diabetic patients in relation to the time of PN. *Difference between diabetic and non-diabetic patients. $^{*}p < 0.05$

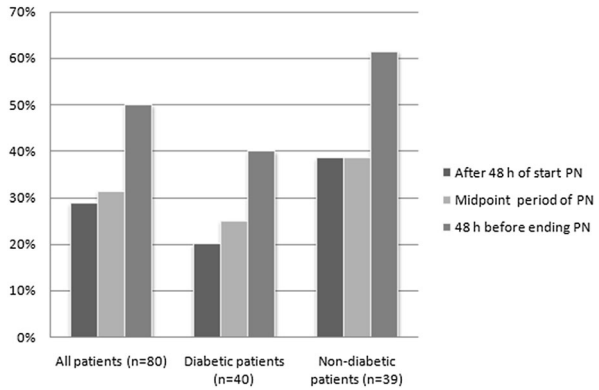

Fig. 2 Proportion of patients with BG < 180 mg/dl in the three study periods

subcutaneous insulin with basal and correction components is an adequate method for achieving and maintaining glucose control in non-critically ill hospitalized patients with PN and extends our knowledge as it was performed during regular clinical practice.

People with DM have a higher probability of requiring surgery during their lifetime than those without DM [21]. In addition, hyperglycemia is a frequent complication of PN in patients both with and without DM. Development of hyperglycemia during PN increases the risk of complications and mortality [7, 22, 23], and several studies have demonstrated that hyperglycemia treatment reduces rates of infections and mortality in surgical patients with diabetes [10, 24, 25].

Studies that evaluate hyperglycemia treatment in patients receiving PN are scarce and include both critically ill and non-critically ill patients. Glycemic targets are heterogeneous, and intervention includes the incorporation of insulin with PN solution [16] and administration of long-acting insulin [19]. Only one study has compared these strategies in surgical patients receiving PN [18], and the results confirm that both glargine insulin and regular insulin in the PN are effective modalities for BG control. Moreover, a recent meta-analysis confirms that the most fitting insulin regimen to treat hyperglycemia in hospitalized patients on nutritional support has not been established [17]. Accordingly, there is a lack of standardized protocols for monitoring and therapy in this population, and strategies are those recommended for hospitalized non-critically ill patients [5, 12, 13, 20, 26].

Although there is no clear evidence for specific BG goals in non-critically ill patients, pre-meal BG targets < 140 mg/dl with random BG < 180 mg/dl are considered reasonable [12, 13, 20, 26]. Glucose management typically involves subcutaneous insulin administered as a basal/bolus/correction regimen with adequate adjustments as the patient's condition changes [12, 13, 20]. In patients on PN, as the rate of glucose infusion is expected to be flat and remain in a postprandial state, a basal plus correction insulin regimen and a BG target < 180 mg/dl were established.

The target BG < 180 mg/dl was achieved in only 50% of patients, equaling overall glycemic control rates obtained in a recent study with glargine insulin (52.24%) and regular insulin in the PN bag (47.76%) [18]. As expected, a high percentage of patients with a previous history of DM did not reach the glycemic target. The average TDD of insulin measured 0.5 U/kg/day in patients with previous DM and 0.37 U/kg/day in those with no history of DM, in accordance with current recommendations for hospitalized patients as initial insulin doses [13, 27, 28]. Therefore, an initial insulin dose estimated at 0.4 U/kg/day seems to be adequate for most patients, and perhaps the main reason for not

achieving reasonable glycemic control was the lack of dose adjustment.

The prevalence of hypoglycemia in patients receiving PN is not well known and has been related to an increase in complications and mortality [29]. The percentage ranges from a low of around 4% up to 40% [30]. In our report, 22.5% of patients experienced BG levels < 70 mg/dl and 7.5% < 40 mg/dl. Most episodes were due to unplanned discontinuation of PN and lack of communication with the endocrinology team, a common occurrence in hospital wards.

The limitations of the present study include a retrospective design that led to exclusion of subjects whose data were incomplete. As the study was performed during regular clinical practice, it provides information on the applicability of a basal-correction insulin regimen in this context. Since our study did not aim to compare different strategies, conclusions regarding the most appropriate method to manage hyperglycemia could not be reached based on this study. Larger studies are needed to determine the optimal glycemic control strategies in patients with PN.

CONCLUSIONS

The results of our study show that in regular clinical practice subcutaneous insulin with basal and correction components is an adequate method for management of hyperglycemia in non-critically ill hospitalized surgical patients with PN.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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