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Randomized Control Trials

Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicenter randomized clinical trial: INSUPAR trial

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SUMMARY

Background: There is no established insulin regimen in T2DM patients receiving parenteral nutrition.
Aims: To compare the effectiveness (metabolic control) and safety of two insulin regimens in patients with diabetes receiving TPN.

Abbreviations used: GI, Glargine Insulin; RI, Regular Insulin; SGA, Subjective Global Assessment; T2DM, Type 2 Diabetes Mellitus; TPN, Total Parenteral Nutrition.

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Design: Prospective, open-label, multicenter, clinical trial on adult inpatients with type 2 diabetes on a non-critical setting with indication for TPN. Patients were randomized on one of these two regimens: 100% of RI on TPN or 50% of Regular insulin added to TPN bag and 50% subcutaneous GI. Data were analyzed according to intention-to-treat principle.
Results: 81 patients were on RI and 80 on GI. No differences were observed in neither average total daily dose of insulin, programmed or correction, nor in capillary mean blood glucose during TPN infusion (165.3 ± 35.4 in RI vs 172.5 ± 43.6 mg/dL in GI; $p = 0.25$). Mean capillary glucose was significantly lower in the GI group within two days after TPN interruption (160.3 ± 45.1 in RI vs 141.7 ± 43.8 mg/dL in GI; $p = 0.024$). The percentage of capillary glucose above 180 mg/dL was similar in both groups. The rate of capillary glucose ≤70 mg/dL, the number of hypoglycemic episodes per 100 days of TPN, and the percentage of patients with non-severe hypoglycemia were significantly higher on GI group. No severe hypoglycemia was detected. No differences were observed in length of stay, infectious complications, or hospital mortality.
Conclusion: Effectiveness of both regimens was similar. GI group achieved better metabolic control after TPN interruption but non-severe hypoglycemia rate was higher in the GI group.
Clinical trial registry: This trial is registered at clinicaltrials.gov as NCT02706119.

1. Introduction

Diabetes mellitus has reached epidemic proportions in most parts of the world [1]. The estimated prevalence of diabetes in Spain is of 14% of the adult population [2]. The prevalence of type 2 diabetes mellitus in the hospital setting is also elevated, and in this case, it is associated with increases in mortality, hospital stay, and costs [3].

Prevalence of diabetes in patients who start total parenteral nutrition (TPN) to either treat or prevent malnutrition is also elevated [4]. Besides, the use of TPN is itself a risk factor for the onset or aggravation of hyperglycemia, regardless of a prior history of diabetes [5]. Values above 180 mg/dL are associated with a greater incidence of complications and death in hospitalized patients who receive parenteral nutrition [4,6]. Difficulty to reach an adequate metabolic control is higher in patients with diabetes mellitus who require parenteral nutrition when compared with patients with prediabetes or stress-induced hyperglycemia, despite receiving higher doses of insulin [7].

The best insulin regimen to use in these patients remains unknown, and few studies have examined the effectiveness and security of the regimens, especially in non-critically ill patients with type 2 diabetes [8–11].

The most prevailing regimen to control hyperglycemia is the introduction of regular insulin added to TPN bags and using subcutaneous Regular insulin as a correction [7,10,12]. This regimen has the advantage that it can deliver the insulin intravenously at a steady rate alongside carbohydrates, reducing the risk of hypoglycemia, and, in malnourished patients with lack of subcutaneous tissue, it may prevent the need for frequent insulin injections.

However other regimens have been proposed, on small scale studies, generally retrospective, including the subcutaneous administration of a long acting insulin such as Glargine [11,13–17], NPH [9], NPL [18], Degludec [19] or non-specified [20]. These new regimens based on long-acting insulins might achieve similar safety and metabolic control [13,14] and, at least theoretically, could reduce glycemic variability, which has been associated with an increase in morbidity and mortality in patients on TPN [21], and facilitate the transition to basal-bolus hospital regimens once TPN is reduced or interrupted [22].

Nevertheless, only three randomized prospective studies have been published, all of them unicenter, small scale, and short studies; and none of those assessed blood glucose control after TPN interruption [13–15]. So new randomized, prospective, and multicenter studies that compare different insulin regimens in non-critically ill patients with diabetes who receive TPN with a higher number of patients and a longer monitoring period are required.

Our hypothesis is that two different insulin regimens (50% Glargine insulin as basal component + 50% Regular insulin as nutritional component versus 100% Regular insulin added to the TPN bag both as basal and nutritional component) could be equally effective and safe during TPN infusion.

The aim of the INSUPAR trial was to compare the effectiveness (metabolic control) and safety of 2 insulin regimens: with or without Glargine as basal insulin in non-critically ill patients with type 2 diabetes who are receiving TPN.

2. Materials and methods

This prospective randomized open-label study was carried out involving 26 centers in Spain (23 university hospitals and 3 non-university hospitals). The study was approved by the Spanish Agency for the Regulation of Drug and Healthcare Products (EUDRACT 2015-003954-42), the Research Ethics Committee provincial of Málaga and of every hospital where the study took place, and registered at clinicaltrials.gov (NCT02706119).

2.1. Patients

The study included adult (>18 years) hospitalized non-critically ill (i.e., patients in non–intensive care unit setting) type 2 diabetes patients who planned to start with TPN (considering it provides more than 70% of the estimated total energy expenditure using Harris–Benedict equation taking into account stress factor) for any cause for at least 5 days between June 2016 and March 2018.

Patients were excluded following these criteria: they were in intensive care units, were type 1 diabetes mellitus or post-total pancreatectomy diabetes, <18 years of age, pregnant, renal failure stage 3b o superior (glomerular filtration rate below 45 mL/min), or with intradialytic parenteral nutrition (Supplementary Table 1).

Patients were considered to have diabetes as assessed according to the international criteria [23]. Blood glucose levels were obtained from capillary and the same glucose meter was provided (Freestyle Optium; Abbott Diabetes Care Inc, Witney, Oxon, United Kingdom) to every center. Hypoglycemia was defined as blood

glucose ≤70 mg/dL and clinically significant hypoglycemia as glucose values <54 mg/dL. Severe hypoglycemia was defined as being associated with severe cognitive impairment regardless of blood glucose level [16,24].

2.2. Randomization and course

Upon establishing the inclusion in the study and signing the informed consent, data of the patients were introduced by each investigator in an online case report form that allocated treatment arms to each patient.

Baseline data were recorded: demographic variables, diagnosis on admission, prior comorbidity (Charlson Comorbidity Index; anthropometric data (weight, height, BMI)); year of diagnosis of type 2 diabetes, and treatment modality, concomitant prescription of hyperglycemic drugs (steroids, somatostatin, tacrolimus or cyclosporine), and nutritional assessment by SGA.

The initial total insulin (between 0.2 and 0.5 UI/kg of actual body with scales of 0.1 UI/kg) was estimated by the physician experience basing on blood glucose prior to the initialization of TPN, age, weight, previous treatment, glomerular filtration rate among others.

Eligible participants were randomized 1:1 to receive one of these two possible insulin regimens:

- Regular insulin group (RI): 100% of insulin requirements administered as Regular insulin (Actrapid HM; Novo Nordisk A/S, Bagsværd, Denmark) added to the bag of TPN as basal and nutritional component.
- Glargine insulin group (GI): 50% of insulin requirements administered as Regular insulin (Actrapid HM; Novo Nordisk A/S, Bagsværd, Denmark) as nutritional component added to the bag of TPN + 50% of insulin administered as subcutaneous Glargine insulin U100 as basal component (Lantus SoloStar; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany or Abasaglar KwikPen; Eli Lilly Nederland B.V, Utrecht, Netherlands).

Blood glucose measurements were performed every six hours until the patient discontinued TPN or up to 15 days at most. We continued to monitor capillary glucose on days 1 and 2 after TPN was stopped.

Blood tests were obtained on day 1, 5 and previous to the interruption of TPN or on day 15 of the study to measure plasma venous glucose. Glycated hemoglobin [25] was measured at day 1.

Adjustments in insulin dose were made according to a previously designed algorithm (Supplementary Fig. 1 & Supplementary Table 2). In both groups, corrections were made subcutaneously with Regular insulin when capillary glucose was above 140 mg/dL. Two-thirds of the total amount of correction insulin was added daily to the previous regimen: in the RI group 100% to the TPN bag and in the GI group 50% to the TPN bag and 50% to the subcutaneous Glargine insulin. If capillary glucose was below 100 mg/dL insulin was lowered according to the above-mentioned algorithm.

2.3. TPN prescription

Total energy expenditure was estimated per Harris–Benedict equation [26] multiplied by a factor ranging between 1.1 and 1.4 in relation to the metabolic stress of the disease. We used actual weight or adjusted weight [27] if BMI was above 25 kg/m^2.

The TPN formulae in all hospitals were provided as a total nutrient admixture ('3 in 1') solution containing carbohydrates, proteins, and lipids. All the TPN patients were seen daily by a member of the hospital Nutrition Unit, who made adjustments in accordance with international guidelines [28–31]. TPN was administered through a central venous line used only for this purpose.

2.4. Outcome measures

Primary endpoint: mean capillary glucose during TPN infusion up to 15 days maximum.

Secondary endpoint:

1) Percentage of capillary glucose above 180 mg/dL.
2) Mean capillary glucose 48 h after TPN interruption.
3) Glycemic variability (standard deviation and variation coefficient of capillary glucose)
4) Rate of hypoglycemia, percentage of patients with hypoglycemia and percentage of capillary glucose below or equal to 70 mg/dL.
5) Complications during hospitalization:
   a) Non-catheter and catheter related bloodstream infections: they were identified as an elevated white blood cell count in addition to one or more of the following: positive blood cultures, chest x-ray suggestive of pneumonia, positive urine culture, postoperative wound infection and use of antibiotics.
   b) Length of stay
   c) In-hospital mortality

2.5. Statistical analysis

Data analysis was performed using SPSS version 22.0 [32]. The Kolmogorov–Smirnov test was used to assess whether the variables were normally distributed or not. We carried out both intention-to-treat and per-protocol analysis. The hypothesis contrast between proportions was done using the χ^2 test with Fisher's exact test, when necessary. Hypothesis contrast for continuous variables between groups used the *t* test for variables that followed a normal distribution, and a non-parametric test (Mann–Whitney or Wilcoxon) for variables that did not conform to normal. Variables tested repeatedly over time (mean capillary glucose) were also analyzed using repeated measures multiple analysis of variance according to time and group. For all calculations, statistical significance was set at $p < 0.05$ for two-tails.

2.6. Sample size

To calculate sample size, we used previous data [7] about non-critically ill diabetic patients who achieved mean blood capillary glucose during PN infusion of 179 ± 46 mg/dL. To detect differences in mean metabolic control during PN infusion of 25 mg/dL between both groups (two tails) with a confidence interval of 95% and a power of 80%, a sample of at least 104 patients is required (52 per group).

3. Results

3.1. Sample

2286 patients with TPN were initially assessed and finally 163 patients with type 2 diabetes were selected to participate and signed the informed consent but 2 of them did not start TPN (Supplementary Fig. 2). 12 patients did not achieve the expected 5 days of TPN.

No differences were observed in any of the baseline features comparing both groups (Table 1): age, gender, renal function, Charlson index, age at diagnosis of diabetes, rate of patients with insulin and other antidiabetic medications prior to admission (Supplementary Table 3), reason for admission, anthropometric parameters, HbA1c and PN formulae.

Table 1
Patient and TPN baseline characteristics.

Variable[a]	RI ($N = 80$)	GI ($N = 81$)	P value
n	80	81	–
Men (%)	71.3	65.4	0.154
Caucasians (%)	100	100	–
Age (years)	71.2 ± 10.8	70.8 ± 9.0	0.127
Glomerular filtration rate (mL/min)	99.2 ± 44.6	95.8 ± 31.3	0.580
Charlson index	7.0 ± 3.1	6.6 ± 2.8	0.457
Type 2 diabetes mellitus			
Duration (years)	10.1 ± 7.3	12.2 ± 8.5	0.152
Age of diagnosis (years)	61.1 ± 11.3	58.6 ± 11.1	0.158
Patients with insulin, *n* (%)	25 (32.1)	21 (25.9)	0.394
Insulin units (UI/kg/day)	0.33 ± 0.86	0.33 ± 0.92	0.930
Patients only with insulin, n (%)	4 (5.0)	7 (8.6)	0.360
Patients only with non-insulin hypoglycemic treatments, n (%)	48 (60.0)	52 (64.2)	0.583
Patients with any antidiabetic drug, n (%)	74 (92.5)	74 (91.4)	0.790
Patients only with diet, n (%)	6 (7.5)	7 (8.6)	0.990
Reason for admission			
Surgical, *n* (%)	44 (55.0)	40 (49.4)	0,745
Oncohematological	22 (27.5)	27 (33.8)	
Medical	14 (17.5)	13 (16.3)	
Anthropometric variables			
Weight (kg)	73.2 ± 18.8	72.1 ± 14.1	0.570
Usual weight (kg)	79.2 ± 19.8	79.2 ± 16.7	0.445
Adjusted weight (kg)	64.7 ± 8.9	65.1 ± 8.9	0.075
Height (m)	1.63 ± 0.09	1.64 ± 0.09	0.368
BMI (kg/m^2)	27.6 ± 6.5	26.8 ± 4.8	0.204
Harris–Benedict (kcal/day)[b]	1290.8 ± 170.2	1308.8 ± 175.0	0.656
Estimated total energy expenditure (kcal/day)	1602.3 ± 218.4	1632.7 ± 242.0	0.375
Subjective global assessment			
Well nourished, *n* (%)	30 (37.5)	22 (27.2)	0.193
Moderate malnutrition, *n* (%)	25 (31.3)	36 (44.4)	
Severe malnutrition, *n* (%)	25 (31.3)	23 (28.4)	
HbA_{1c}			
%	6.6 ± 1.0	6.6 ± 1.1	0.456
mmol/mol	49.5 ± 12.5	48.2 ± 11.4	0.494
TPN characteristics			
Days with TPN (days)	9.7 ± 6.8	10.5 ± 7.4	0.883
Mean daily carbohydrates in PN (g)	185.5 ± 31.1	188.3 ± 31.9	0.583
Mean daily amino acids in PN (g)	80.7 ± 13.3	82.5 ± 14.6	0.652
Mean daily lipids in PN (g)	57.0 ± 11.4	56.2 ± 12.4	0.709
Mean daily carbohydrates in PN (g/kg[b])	2.82 ± 0.42	2.84 ± 0.44	0.554
Mean daily carbohydrates in other fluids (g)	2.87 ± 6.9	4.26 ± 8.1	0,156
Mean daily amino acids in PN (g/kg[b])	1.23 ± 0.19	1.24 ± 0.18	0.482
Mean daily lipids in PN (g/kg[b])	0.87 ± 0.18	0.85 ± 0.19	0.431
Mean daily kcal PN (kcal/day)	1638.3 ± 225.5	1647.8 ± 229.9	0.980
Total mean daily kcal PN + in other fluids (kcal/day)	1659.9 ± 237.2	1674.7 ± 243.9	0.872
Hyperglycemic drugs			
Corticosteroids, *n* (%)	17 (21.3)	9 (11.1)	0.080
Tacrolimus, *n* (%)	0 (0.0)	1 (1.2)	0.319
Somatostatin, *n* (%)	7 (8.8)	5 (6.2)	0.534
Any drug that induces hyperglycemia[c], *n* (%)	22 (27.5)	15 (18.5)	0.176

[a] Values are mean ± SD unless otherwise stated.
[b] We used actual weight or adjusted weight if BMI was above 25 kg/m^2.
[c] This includes the number of patients that were on any hyperglycemic drug; in the RI group there were two patients with both Corticosteroids and Somatostatin.

3.2. Metabolic control

No statistically significant differences were observed comparing mean values of different glycemic parameters (venous blood glucose, capillary glucose, glycemic variability parameters, total insulin and capillary glucose decrements) neither during TPN infusion nor on each day of the study (Supplementary Table 4). Using repeated measures multiple analysis of variance, we found significant differences in relation to time (a linear decrease) in both groups. No differences were observed between groups neither in mean capillary glucose nor in the descent of capillary glucose with respect to the first day.

There were statistically significant differences in the rate of capillary glucose ≤70 mg/dL, the number of hypoglycemic episodes per 100 days of TPN and in the percentage of patients with non-severe hypoglycemia (higher on GI) (Table 2). However, none of the groups had any severe hypoglycemia episodes.

Two days after the interruption of TPN, we observed significantly lower mean capillary glucose levels on GI group vs RI.

No other statistically significant differences were observed between the two groups regarding complications (Table 3).

When data were analyzed per-protocol (excluding 12 patients that did not reach 5 days of TPN) the variables were still statistically significant.

4. Discussion

Our study is the first multicenter randomized clinical trial that assesses the effectiveness and safety of two different modalities of insulin therapy in non-critically ill diabetic patients who receive PN with a long follow-up and a monitoring period following its interruption.

Both regimens (50% Glargine insulin as basal component + 50% Regular insulin as nutritional component versus 100% Regular insulin added to the TPN bag both as basal and nutritional component) are equally effective to reach an adequate metabolic control during PN infusion.

Clinical practice guidelines and consensus statements recommend a target glucose range of 140–180 mg/dL for the majority of non-critically ill patients, but more stringent goals may be appropriate for selected patients if this can be achieved without significant low blood glucose events [8,33]. During PN mean total capillary glucose, glycemic variability, and insulin dose were similar in both groups without finding significant differences in any day (Supplementary Table 4). We did not find differences in the percentage of measurements above 180 mg/dL, values that have been associated with an increase in morbidity and mortality [4,6,34], or from 100 to 180 mg/dL. These results are in accordance to the previously published randomized studies which compared subcutaneous Glargine versus Regular insulin added to PN in people with diabetes [13,14,35].

As well as other authors [14], we have observed a tendency to have higher capillary glucose in GI group during the first days of TPN (the goal of reaching mean capillary glucose below 180 mg/dL could only be reached after three days in GI. On the contrary, RI achieved it on the first day). Nonetheless, we did not observe differences in metabolic control at different moments of the day between groups. Metabolic control was significantly better in GI on the 48 h after the interruption of PN; Glargine insulin pharmacodynamics, with a duration of action close to 24 h, could explain this difference.

Mean glycemic control reached with both regimens was similar to the results published in other prospective studies in patients with diabetes and PN (Supplementary Table 4) [13,14] or mildly superior to the one achieved with insulin pumps [15]. Our results are clearly better than the ones obtained in patients with hyperglycemia treated only with subcutaneous insulin regimens (basal plus correction insulin regimen, with no insulin added to PN bag) [17,20]. Despite this, one third of the patients showed a percentage

Table 2
Outcomes - metabolic control.

Variable[a]	RI ($n = 80$)	GI ($n = 81$)	*P* value
Insulin			
Mean total daily insulin (IU)	44.2 ± 25.3	48.9 ± 25.8	0.412
Mean correction daily insulin (IU)	9.9 ± 8.0	11.5 ± 7.8	0.113
Mean total daily insulin (IU/kg)	0.62 ± 0.32	0.69 ± 0.37	0.321
Mean correction daily insulin (IU/kg)	0.14 ± 0.12	0.16 ± 0.1	0.095
Mean total daily insulin/10 g of carbohydrates in TPN (IU)	2.4 ± 1.1	2.6 ± 1.4	0.156
Mean capillary glucose			
08:00 h (mg/dL)	163.4 ± 36.1	169.2 ± 45.0	0.374
13:00 h (mg/dL)	169.6 ± 37.1	178.5 ± 46.9	0.187
20:00 h (mg/dL)	167.6 ± 38.3	169.4 ± 45.5	0.795
00:00 h (mg/dL)	155.5 ± 38.4	167.9 ± 47.0	0.087
During TPN (mg/dL)	165.3 ± 35.4	172.5 ± 43.6	0.250
Mean post-TPN capillary blood glucose 48 h (mg/dL)	160.3 ± 45.1	141.7 ± 43.8	**0.024**
Mean Day 1 post-TPN capillary glucose (mg/dL)	161.3 ± 47.7	143.1 ± 53.8	0.054
Mean Day 2 post-TPN capillary glucose (mg/dL)	160.6 ± 47.3	143.3 ± 39.8	**0.046**
Hypoglycemic variables			
Number of patients with capillary glucose ≤ 70 mg/dL, *n* (%)	9 (11.2%)	22 (27.2%)	**0.016**
Number of patients with capillary glucose < 54 mg/dL, *n* (%)	1 (1.2%)	7 (8.8%)	0.064
Number of severe hypoglycemia, *n* (%)	0	0	
Number of hypoglycemia events/100 days of TPN	1.9 ± 6.1	4.9 ± 9.8	**0.015**
Capillary glucose %[b]			
≤70 mg/dL (%)	0.8 ± 3.0	1.8 ± 3.5	**0.011**
71–100 mg/dL (%)	7.5 ± 10.4	7.0 ± 8.9	0.913
101–140 mg/dL (%)	29.2 ± 20.3	27.6 ± 23.3	0.430
141–180 mg/dL (%)	29.8 ± 16.1	26.4 ± 16.0	0.163
71–180 mg/dL (%)	66.7 ± 27.7	61.2 ± 30.0	0.227
>180 mg/dL (%)	32.7 ± 27.2	37.2 ± 30.5	0.435
Standard deviation of capillary glucose (mg/dL)	40.4 ± 16.0	43.4 ± 19.0	0.292
Variation coefficient of capillary glucose (%)	24.5 ± 8.1	25.5 ± 10.2	0.570

Bold signifies P-value below 0.05 ($p < 0.05$).
[a] Values are mean ± SD unless otherwise stated.
[b] Based on the total capillary glucose carried out during TPN infusion.

of measurements above 180 mg/dL, results similar to those found by our group previously in people with diabetes [7].

The insulin regimen and monitoring system should also minimize glycemic variability [36], as it has been associated with increased hospital mortality during TPN but not in people with diabetes [21]. Both variation coefficient and standard deviation of capillary glucose were similar in both groups and with similar results to those published by other authors [14,15].

The number of hypoglycemic events was significantly higher in GI, nevertheless, all of them were mild and none of them were severe.

Insulin added to TPN bag has the advantage that it can deliver the insulin intravenously at a steady rate alongside carbohydrates reducing the risk of hypoglycemia [10]. In a previous study published by our group in non-critically ill patients with PN [37] the rate of low blood glucose events (<70 mg/dL) was clearly inferior (only 0.8 per 100 days of PN and occurred in 6.8% of the patients) to the one observed in our current study, especially in GI group (Supplementary Table 4); however only 21.6% of the assessed cases presented diabetes.

Table 3
Outcomes - complications.

Variable[a]	RI ($N = 80$)	GI ($N = 81$)	*P* value
Length of stay (days)	31.1 ± 26.0	29.8 ± 22.0	0.870
Mortality (n, %)	11 (13.8)	13 (16.0)	0.682
Infectious complications			
CLASBI[b], *n* (%)	12 (15.0)	76 (5.0)	0.078
Sepsis, *n* (%)	7 (8.8)	3 (3.7)	0.210
Pneumonia, *n* (%)	3 (3.8)	3 (3.7)	1.000
Surgical site infection, *n* (%)	8 (10.0)	5 (6.3)	0.564
Urinary tract infection, *n* (%)	1 (1.3)	4 (4.9)	0.367

[a] Values are mean ± SD unless otherwise stated.
[b] Central line-associated bloodstream infections.

Hakeam et al. [14] were the only group describing a lower percentage (although non-significant) of hypoglycemic events in patients with diabetes and PN in Glargine group (5.7%) versus Regular insulin added to PN (11.4%); lesser duration of the study (only 6 days after randomization) might partially explain the differences. Li et al. [15], comparing subcutaneous Glargine versus subcutaneous continuous insulin infusions in patients with diabetes receiving PN, did not observe any severe hypoglycemia. Oghazian et al., in stable critically ill patients with diabetes, did observe a higher number of non-significant hypoglycemic events in Glargine group during a period of 3 days [13]. Neff and Ramos et al. [17,20] described low blood glucose events in patients with PN and hyperglycemia treated only with subcutaneous insulin in 29% and 22% of the cases, respectively; sudden interruption of PN as well as higher duration of PN [20] could be some of the factors that increase the risk of hypoglycemia [37] in these patients. The percentage of hypoglycemia might reach up to 40% of the patients with PN and hyperglycemia treated with infused intravenous insulin [21].

We did not observe any differences in number of infectious complications, length of stay or mortality (Table 3).

Similar to hyperglycemia, hypoglycemia is associated with increased in-hospital mortality but the risk might be limited to patients with spontaneous hypoglycemia and not to patients with drug-associated hypoglycemia [38]. We did not observe differences in mortality, length of stay or other complications between groups, maybe because of the absence of severe hypoglycemia.

It is well established that an elevation in blood glucose is a risk factor for infection [39]. Unlike other authors [13,14] that only evaluated glycemic control, we have also assessed the incidence of infectious and non-infectious complications but we did not find any significant differences in any of these variables. Mortality was also evaluated and it was similar in both groups, these figures are in agreement with those previously published by us in subgroups of people with diabetes [4].

Our study is, among the others of its kind, the one with the largest number of patients recruited and the only one that is multicenter. Besides, it includes a very homogeneous sample of patients (all of them previously diagnosed with type 2 diabetes mellitus, none with stress hyperglycemia and with very similar composition of the TPN bags), it evaluates the use of insulin during 15 days of PN, it continues the follow-up 48 h after the interruption of the PN, and it also includes the assessment of complications.

However, there are some limitations. First of all, the recruitment was variable (from 1 to 15 patients) so the low recruitment of some centers might have affected the analysis. There is also the fact that we focus on non-critically ill patients with type 2 diabetes mellitus, therefore we cannot apply these conclusions to another group of patients; nevertheless we have chosen these patients because they are the most difficult ones to control in previously published studies [7]. Sample size was calculated to detect differences in mean capillary glucose but not in complications so the conclusions regarding complications should be taken cautiously. Besides, although we have made an ample number of statistical comparisons, the parameters that reach significance (hypoglycemic events and metabolic control after the interruption of PN) are concordant. And finally, of the 161 patients who started TPN, 12 of them did not reach 5 days of treatment, however, the results were still

statistically significant as both intention-to-treat and per-protocol analysis.

In conclusion, we have observed that both regimens (50% subcutaneous Glargine as basal component + 50% Regular insulin as nutritional component versus 100% Regular insulin added to total parenteral nutrition bag (basal and nutritional component)) are similar in relation to its effectiveness to achieve an adequate metabolic control during PN infusion in non-critically ill patients with diabetes so both regimens could be used. Nevertheless, GI group achieved better metabolic control after TPN interruption and non-severe hypoglycemia rate was higher in the GI group. These data indicate that in patients with 100% Regular insulin added to TPN bag, Glargine may improve the transition and control after its interruption if it is prescribed previously [22].

This study opens the way for other clinical trials that might evaluate other insulin regimens and in other group of patients with hyperglycemia and PN.

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Authors' contributions

G.O. substantially contributed to the conception and design of the study, acquisition, analysis, and interpretation of the data; statistical analysis; and drafting of the manuscript. J.A. contributed to the acquisition, analysis, and interpretation of the data; statistical analysis; revised the article for important intellectual content and drafting of the manuscript. R.L., S.H., J.M.G.A, K.G., M.F., E.C., L.M.L.P, J.A., C.A., M.J.O., A.G.M., I.B., P.S.A., N.P.F., J.J.L.G., J.O., C.A., C.T., J.D.M., S.G., A.L.A., M.R.A., A.Z., J.P., and S.T. contributed to the data acquisition and critical review of the manuscript. M.J.T. substantially contributed to the design of the article; data acquisition; and critical review of the manuscript.

G.O. and J.A. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.02.036.

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