Original article

Clin Ter 2014; 165 (1):e17-23. doi: 10.7417/CT.2014.1666

Use of neutral protamine lispro insulin (NPL) in patients with hyperglycemia receiving parenteral nutrition

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Abstract

Aims. Nutritional support with parenteral nutrition (PN), a key component in the care of critically ill patients, usually requires insulin therapy in patients with diabetes or may require insulin treatment in patients not known to be diabetic. We wanted verify whether it is possible to use neutral protamine lispro (NPL) in double administration monotherapy in patients receiving artificial nutrition (AN) and if the same NPL is capable of obtaining and maintaining acceptable glycemic control without inducing hypoglycemia.

Patients and Methods. We studied 18 consecutive patients, who were not taking insulin, they needed to start artificial nutrition, and presenting at least two consecutive blood glucose > 120 mg/dL. Each patient was given at least 1 U of insulin for every 10 grams of glucose infused.

Results. Eighteen consecutive patients, not stratified in any way, were judged eligible in the last 24 months, with a mean age of 71 years (range 54–85 yrs). All patients were evaluated after 2, 3 and 5 days of treatment; only 1 patient has not been evaluated to 5 days. Mean glycemic values on days 2, 3, 5 were in range between 145 and 180 mg/dL. Any adjustments in NPL dose were carried out by the team of nutrition and there was no hypoglycemia that required medical intervention in emergency.

Conclusions. Our impression is that also lispro protamine insulin (NPL) in double subcutaneous administration may contribute to improving the glycemic values in patients receiving parenteral nutrition with hyperglycemia. ***Clin Ter 2014; 165(1):e17-23. doi: 10.7417/CT.2014.1666***

Key words: *artificial nutrition, hyperglycemia, insulin, neutral protamine lispro insulin, parenteral nutrition*

Introduction

Artificial Nutrition (AN) is a therapeutic procedure for people on where oral feeding is not feasible and/or not enough to meet the needs calorie protein or it is contraindicated. The AN is indicated in the prevention and treatment of malnutrition and in meeting the increased caloric needs typical of the states of hypercatabolism. Poor nutritional status or moderate-to-severe nutritional risk results in about 50% prolongation of hospital stay (1). Nevertheless, malnutrition remains a largely unrecognised problem in hospital and highlights the need for education on clinical nutrition. The prevention and treatment of hospital malnutrition offers an important opportunity to optimize the overall quality of patient care, improve clinical outcomes, and reduce costs (2). Parenteral Nutrition (PN) is the way of administration of nutrients intravenously (into a peripheral or central vein). Nutritional support with parenteral feeding usually requires insulin therapy in patients with diabetes or may requires insulin treatment in a patient not known to be diabetic.

Hyperglycemia is considered the main hindrance to the activation of a correct nutritional support, even in patients not affected by diabetes. The connection between hyperglycemia, possible infections and/or an increase in mortality is well known in critically ill patients, independently of the fact that the patients are diabetic or suffer from hyperglycemia correlated with their illness (3, 4). Stress hyperglycemia is an independent predictive factor for in-hospital complications after acute coronary syndrome in diabetic and nondiabetic patients(5).The risk of congestive heart failure or cardiogenic shock is also increased in patients without diabetes (6). Recently it has been shown that hyperglycemia (mean blood glucose level >180 mg/dL) in noncritically ill patients who receive TPN is associated with a higher risk of in-hospital mortality (7). Usually, AN, whether enteral or parenteral, is considered one of the main causes of hyperglycemia in hospitalized patients. This leads to two other problems, which are overfeeding (8, 9) and insulin administration. The normalisation of glycemic levels improves the prognosis even if the best therapeutic strategy has still not be found. Anyway, most of the patients do not receive a nutritional support proportionate to the body's request of calories; malnutrition is so even more stressed by a poor glycometabolic compensation. Only recently doctors have tried to focus on such problem, which was pointed out for the first time in the late 1936 (10-12), when Studley published an article called "Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer". Parenteral nutrition

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ISSN 1972-600

enables to administer via vein all nutritional components to the patients who cannot attain an adequate oral intake, but the most frequent short term problem is undoubtedly hyperglycemia. Managing some of the many existing protocols for intensive insulin therapy can be difficult (13,14): on the other hand, literature on the management of non critical patients seems to be very poor. The commercialization of insulin analogs has been a very good answer for ambulatory diabetic patients, yet their use in artificial nutrition has been quite unfrequent up to now. The Italian Dietetic and Clinical Nutrition Association (ADI) and the Association of Diabetologists (AMD) have published specific recommendations (15) on insulin treatment during artificial nutrition providing for the possible use of a long acting analogue insulin in the patient stabilized. Diabetic patients or non-diabetic patients showing two consecutive glycemic values >120 mg/dL in PN can be given 0,1 U of insulin per gram of glucose. If in the next 24 hours the glycemic levels are too high, they can be adjusted with some regular insulin, i.e., 0.05 U per each gram of glucose. There are limited reports on the possible use of insulin lispro in a suspension together with protamine sulphate in double subcutaneous administration (16). The authors report their experience with a protocol that calls for the use of neutral protamine lispro in patients requiring parenteral nutrition and that opens interesting prospects for clinical practice.

The purpose was to verify whether it is possible to use neutral protamine lispro (NPL) in double somministration monotherapy in patients receiving artificial nutrition (AN) and if the same NPL is capable of obtaining and maintaining acceptable glycemic control without inducing hypoglycemia. The primary outcome to be studied is the frequency and severity of hyperglycemia and hypoglycemia.

Materials and Methods

The sample is made up of patients receiving parenteral nutrition, diagnosed diabetics and non-diabetics, receiving treatment at the Diabetology, Dietetics and Clinical Nutrition Unit, who are hospitalized. The usual insulin treatment, staying in intensive care, and treatment with steroids at high dosages were considered criteria for exclusion. The study included 18 consecutive patients, men and women age > 18 years, who were not taking insulin, who need to start artificial nutrition, who had submitted at least two consecutive blood glucose >120 mg/dL. Only two patients had a history of diabetes controlled by diet alone. All patients were to be given subcutaneous neutral protamine lispro insulin in double subcutaneous administration at a dose of 0.1 units of insulin per gram of glucose infused and 0.15 units higher blood sugar levels >150 mg/dL. The following were considered measurable parameters:

- age
- starting BMI and HBA1c;
- at least 6 glycemic measurements (every 4 hours starting at midnight) and glycemic mean on the day preceding the start of treatment with NPL and parenteral nutrition;
- 6 glycemic measurements and glycemic mean on the three days following the start of treatment with NPL and on day 5 (every 4 hours starting contemporary at PN);
- glycemic oscillations in the days considered and number of hypoglycemias found;
- daily ketonuria and electrolytes (sodium, potassium and magnesium);
- glycemic control definitions according to Italian standard for the care of the diabetes;
- albuminuria;
- lymphocytes count.

The TPN called for infusion for 24 h through a central catheter (CVC) of an industry-prepared, three-compartment, 1600-1800 Kcal “all-in-one” bag with approximately 200 g of carbohydrates.

Procedures

At the Terni Hospital, AN is indicated in all wards, with the exception of Intensive Care, by the doctors of the Diabetology, Dietetics and Clinical Nutrition Unit, who are also responsible for prescribing the type of nutrition and the treatments connected with it. In practice, AN is centralized also as regards the storage and distribution of PN bags. Once total PN was indicated and the conditions for inclusion and exclusion were verified, the doctors activated the protocol and indicated the sample-taking times and procedures and verified that each medical file contained the final report.

Patients

Eighteen consecutive patients, not stratified in any way, were judged eligible in the last 24 months, with a mean age of 71 years (range 54–85 yrs). All patients were evaluated after 2 days of treatment and on day 3 and 5, only 1 patient has not been evaluated to 5 days**.** The high number of patients who finished the study results from the fact that the doctors of single team give the indications for different wards and prescribe both nutritional and insulin treatment. The double subcutaneous administration was not considered an obstacle by the staff of the departments of the hospital. Any adjustments in insulin dose were carried out by the team of nutrition and there were no hypoglycemia that required medical intervention in emergency.

Results

Table 1 shows the characteristics of the sample, the reason for admission, the membership department and units of insulin administered the first and fifth days of artificial feeding. On average were administered on the first day of parenteral nutrition 22.7 units of insulin to the patient and after five days 26.2 u. Glycemic measurements on the day preceding the start of treatment with NPL and parenteral nutrition are listed in Figure 1. Glycemic measurements on the day 2 and mean glycemic values on the day 0, 2, 3, 5 are listed in figures 2, 3, 4 and in table 2. Mean glycemic values on days 2, 3, 5 were in range between 145 and 180 mg/dL. Mean of daily glycemic values progressively decreases; T test is statistically significant for day 0 vs day 3 ($p< 0.05$) and for day 0 vs day 5 ($p <0.01$).

Table 1. Characteristics of the sample.

Pt n.	Age	Sex	Ward	Diagnosis	Diab.	NPL U. day 1	NPL U. day 5
1	58	m	Neurology	Cerebral anoxia, CIC, heart failure	no	30	30
2	80	f	Geriatric	Intestinal perforation, stroke	no	20	20
3	83	f	Liver Unit	Intestinal perforation	no	16	16
4	79	m	Liver Unit	Gastric cancer	no	16	16
5	79	f	Surgery	Biliary tract cancer	no	50	80
6	75	f	Oncology	Peritoneal carcinomatosis	yes	20	20
7	70	m	Neurology	Respiratory failure	no	20	20
8	78	m	Surgery	Hemorrhagic pancreatitis	no	30	50
9	58	f	Liver Unit	cholecystectomy	no	32	36
10	69	m	Surgery Unit	Obstructive jaundice	no	28	28
11	85	m	Hepatobiliary Surgery	Bowel obstruction	no	20	20
12	82	f	Emergency surgery	Bowel obstruction	no	20	20
13	81	f	Liver Unit	Pancreatic cancer	no	20	20
14	37	f	Oncology	Breast cancer	no	20	20
15	54	m	Cardiology	Heart failure	no	20	28
16	81	f	Surgery Unit	Intestinal cancer	yes	12	12
17	72	f	Surgery Unit	Biliary tract cancer	no	16	16
18	60	m	Emergency surgery	pancreatitis	no	20	20

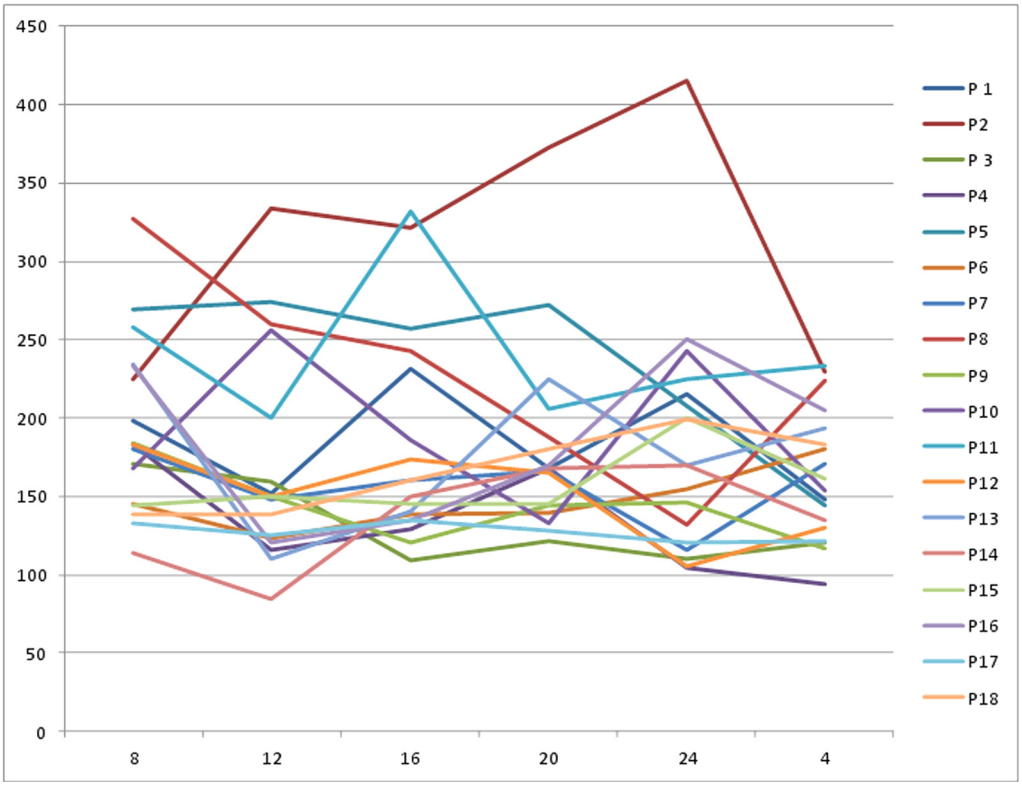

Fig 1. (every 4 hours) glycemic measurements on the day preceding the start of treatment with NPL and parenteral nutrition.

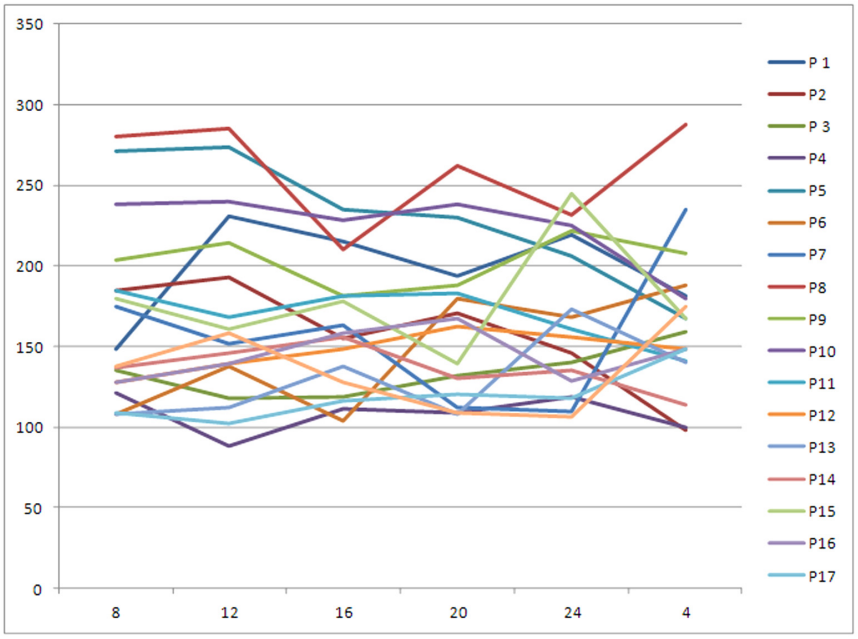

Fig. 2. (every 4 hours) glycemic measurements on the day 2 after the start of treatment with NPL and parenteral nutrition.

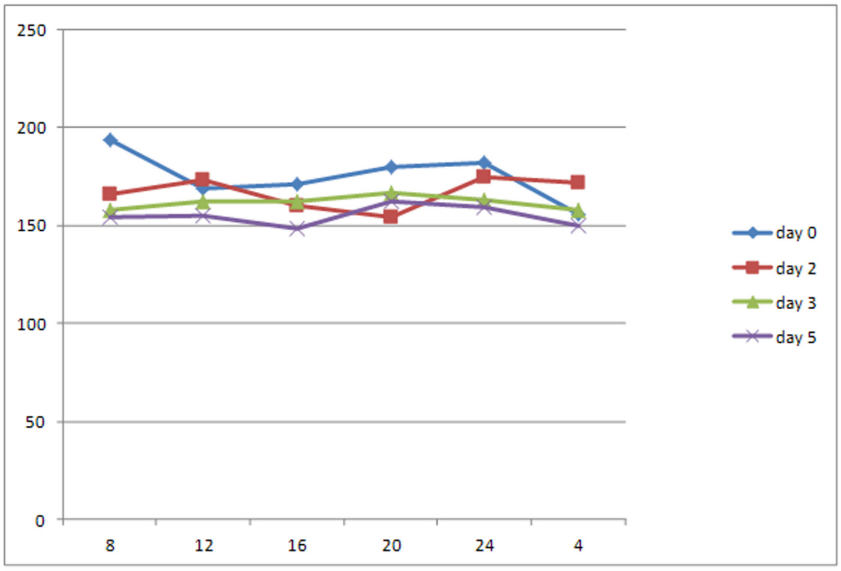

Fig. 3. Mean glycemic values (every 4 hours) on days 0, 2, 3. 5.

Table 2. Mean glycemic values on days 0, 2, 3, 5 (every 4 hours) and standard deviation (SD).

Time (hour)	Day 0	Day 2	Day 3	Day 5	Overall SD	Days 2,3,5 SD
8	194	166	158	154	15.62	4.99
12	169	173	162	155	6.87	7.41
16	171	160	162	148	8.20	6.18
20	180	154	167	162	9.44	5.35
24	182	175	163	159	9.20	6.80
4	156	172	158	150	8.06	9.09

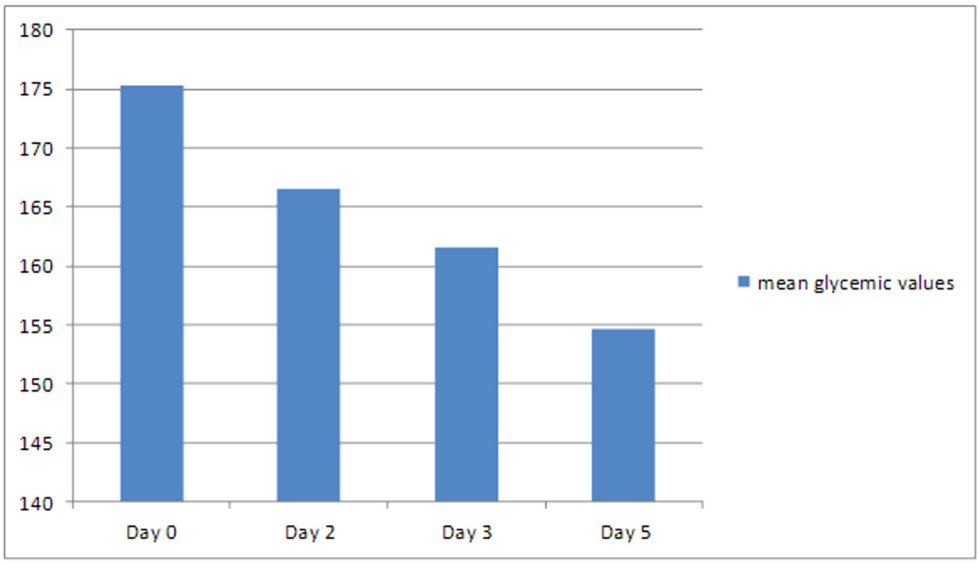

Fig. 4. Mean glycemic values (daily) on days 0, 2, 3, 5.

Discussion

The recurrent problem during artificial nutrition is a glycemic alteration, in lack or in excess (17). Hyperglycemia in patients under PN can depend on the rapid administration of the infused nutrients, on their quality and quantity and also on the pathology that led the patient to his hospitalization. Very often, patients that need a nutritional support, for fear of hyperglycemic attacks run the risk for hyponutrition (18), and also are given an insufficient insulin treatment for fear of hypoglycemic attacks. Stress hyperglycemia is an independent predictive factor for in-hospital complications in diabetic and nondiabetic patients. The treatment of patients with type 2 diabetes in the hospital is very different from their treatment at home. The particular conditions and comorbidities that can arise in the hospital necessitate flexible, individualized strategies for lowering blood glucose concentration (19). The commercialization of insulin analogs has changed the treatment of ambulatory diabetic patients (20). On the other hand, they are not much used in AN, despite the availability of slow-acting and flat action profile insulin analogues. Glycemic values at the beginning of nutritional treatment are kept under 200 mg/dL, even if the purpose is to reach low glycemic values, less than 150 mg/dL in the absence of ketonuria or other complications like dehydration or hyperosmolarity. Literature shows that the initial correct levels of sugar in order to prevent overfeeding should be about 150-200 g per day. Some Authors assume that under PN carbohydrate levels higher than 4-5 mg/kg/min or 20-25 kcal/kg/per day could exceed the glucose oxidation ability, leading to severe hyperglycemia attacks, lypogenesis and steatosis (21). Insulin treatment should always go hand in hand with an adequate parenteral infusion and should also keep glycemic levels acceptable. Hyperglycemia is undoubtedly an important negative prognostic factor and also a predictive potentially modifiable factor. Morbility and mortality in surgical intensive care units drastically reduces when glycemic levels are kept under 110 mg/dL; also, all Authors agree on the need to develop insulin infusion protocols which should stabilize within 24 hours the glycometabolic state. Glycemic values up to 180 mg/dL during continuous glucose solution infusions are usually considered as intermediate or acceptable values; nevertheless, in a critical situation Finney et al. considers acceptable only values up to 144 mg/dL and optimal glycemic levels between 80 and 110 mg/dL (11). In the NICE-SUGAR Study international, randomized trial, investigators found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per decilitre resulted in lower mortality than did a target of 81 to 108 mg per decilitre (22). In this trial, more patients in the intensive-control group than in the conventional-control group were treated with corticosteroids, and the excess deaths in the intensive-control group were predominantly from cardiovascular causes. Recently a meta-analysis of all studies published up to 2009 has confirmed that intensive treatment of blood glucose does not improve mortality, increasing the risk of hypoglycaemia (23). The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) recommends to keep blood sugar between 140 and 180 mg/dL and fall below. According to ADI-AMD recommendations a glycemic range is considered intermediate if between 145 and 180 mg/dL and moderate between 181 and 200. The days after the acute event less attention is paid to the importance to ensure a proper insulin support and a proper nutrition in order to prevent risks: moreover, only a few studies showed the possibility of a long-acting insulin analog treatment of hyperglycemia during artificial nutrition in stabilized patients. The use of these analogs may also be useful to tamper with PN bags as little as possible. Unfortunately these bags are often tampered with and the insulin is added directly into them, although the pharmaceutical industry clearly indicates the risks by doing so. The three currently marketed long-acting insulin analogs, glargine, detemir and insulin lispro protamine suspension (NPL), represent the most significant

advances in basal insulin supplementation since the 1940s and 1950s and the introduction of the intermediate-acting NPH (neutral protamine Hagedorn) insulin (24). In the subject stabilized that enteral or parenteral nutrition practice with peristaltic pump was used subcutaneous insulin glargine (25, 26), with favorable results. Also ADI-AMD recommendations (15) underline that a long-acting insulin analog can be used on a stabilized patient supported with PN via peristaltic pump; they also stress the importance that any addition to the bags has to be done under aseptic conditions and preferably under a laminar-flow hood and has to be checked and validated. Knowledge of drug compatibility is needed before adding drugs to the PN bags, as mentioned in the drug datasheet. As regards insulin, only human regular insulin is compatible with PN formulations. A 1-unit-per-10-grams-of-carb (1:10) ratio led to glycometabolic values usually considered acceptable. In patients with a history negative for diabetes and in those with diabetes you can start with 0.1 units of insulin per gram of glucose infused (1 IU per 10 g of glucose) and 0.15 units if blood sugar levels are higher than 150 mg/dL. People with type 2 diabetes and obese may need also to 0.2 units of insulin for every gram of glucose, whereas in those with type 1 diabetes and lean, insulin requirements may shrink up to the value of 0.05 units per gram of glucose. In patients with fever, severe trauma or other situations of particular stress which increase insulin resistance you can start with 0.2-0.3 IU of insulin per g of glucose (2-3 UI/10 g glucose). If the 24 h blood sugar levels are above 140 mg/dL can adjustments to be made by increasing the infusion of regular insulin of 0.05 units per gram of glucose (2, 4, 15). Our report shows that also NPL lispro insulin s.c., (27), can be used in patients under parenteral nutrition who need an insulin treatment and who can use a constant-flow infusion pump. It is always important to accurately study each single case report, but previous experiences with long-acting insulin analogs undoubtedly show that flat insulin curves can be used on this kind of patients (28-30), if stabilized. Even more important is that these analogs do not cause significant oscillations of glycemia, unlike other insulins, thus reducing the medical assistance of doctors and nurses and the need of rapid-acting insulin injections prescribed by the duty doctor. This is all the more interesting considering that glycemic control of patients under parenteral nutrition is worse than in patients under enteral nutrition; also, hyperglycemia adversely affects clinical outcomes (31-33). The objective of our study was to demonstrate the possibility of treatment with neutral protamine lispro insulin for patients receiving parenteral nutrition. Insulin lispro protamine suspension (NPL) is a protamine-based, intermediate-acting insulin formulation of the short-acting analog insulin lispro: insulin lispro (LysB28, ProB29 human insulin) is formed by switching lysine and proline amino acids at positions B28 and B29. In recent randomized controlled trials of insulin-naïve patients with type 2 diabetes, NPL achieved similar glycemic control compared with other basal insulin analogs (27, 34). Erroneously, at least in Italy, patients who are not in intensive care are not considered critically ill, even if they need to be fed artificially. In our opinion, regardless of the ward they are in, a patient receiving AN should be considered critically ill and treated accordingly. In addition, the need to tamper as little as possible with TPN bags and to ensure an insulin steady state is habitually underestimated. Reducing glycemic oscillations brings about a reduction in the number of times medical and nurse assistance is required and the number of insulin pushes prescribed by the doctor on duty. The data we obtained and the good acceptability of the protocol by all wards seems to justify the use of NPL in PN as well. The double subcutaneous administration was not considered an obstacle by the staff of the departments of the hospital and there were no hypoglycemia that required medical intervention. Not having stratified the patients in any way is further proof of the manageability and possibilities for using the analogue.

In conclusion, nutritional support with parenteral feeding, a key component in the care of critically ill patients, usually requires insulin therapy in patients with diabetes or may require insulin treatment in patients not known to be diabetic. Our impression is that also lispro protamine insulin (NPL) may contribute to improving the glycemic values in patients receiving AN with hyperglycemia. The development of hyperglycemia during parenteral nutrition is associated with an increased risk of death; there are no specific guidelines recommending effective strategies (35). Randomized controlled studies are needed to evaluate safe and effective therapeutic strategies. It is important to remember that we must look for the appropriate treatment for each patient and that one protocol may not suffice for all patients

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