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

G. Fatati¹, I. Grandone¹, M. Palazzi¹, P. Weber², E. Mirri¹

Units of ¹Diabetology, Dietology and Clinical Nutrition, and ²Health Management, “S. Maria” Hospital, Terni, Italy

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.

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 caloric 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...
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 hyper-
glycemia. 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 Diabetic and Clinical
Nutrition Association (ADI) and the Association of Diabe-
tologists (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 hypoglyce-
mia. 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, Diietetics and Clinical Nutri-
tion 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 consecu-
tive 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;
- 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 eval-
uated 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 hypoglycemias that required
medical intervention in emergency.

Results

Table 1 shows the characteristics of the sample, the rea-
son 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.

<table>
<thead>
<tr>
<th>Pt n.</th>
<th>Age</th>
<th>Sex</th>
<th>Ward</th>
<th>Diagnosis</th>
<th>Diab.</th>
<th>NPL U. day 1</th>
<th>NPL U. day 5</th>
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<td>1</td>
<td>58</td>
<td>m</td>
<td>Neurology</td>
<td>Cerebral anoxia, CIC, heart failure</td>
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<td>30</td>
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<td>2</td>
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<td>f</td>
<td>Geriatric</td>
<td>Intestinal perforation, stroke</td>
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<td>f</td>
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<td>m</td>
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<td>Gastric cancer</td>
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<td>5</td>
<td>79</td>
<td>f</td>
<td>Surgery</td>
<td>Biliary tract cancer</td>
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<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>f</td>
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<tr>
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<td>8</td>
<td>78</td>
<td>m</td>
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<td>50</td>
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<tr>
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<td>f</td>
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<td>32</td>
<td>36</td>
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<tr>
<td>10</td>
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<td>Obstructive jaundice</td>
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<td>28</td>
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<tr>
<td>11</td>
<td>85</td>
<td>m</td>
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<td>Bowel obstruction</td>
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<td>20</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>82</td>
<td>f</td>
<td>Emergency surgery</td>
<td>Bowel obstruction</td>
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<td>20</td>
<td>20</td>
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<tr>
<td>13</td>
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<tr>
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<tr>
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<tr>
<td>16</td>
<td>81</td>
<td>f</td>
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<td>12</td>
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<tr>
<td>17</td>
<td>72</td>
<td>f</td>
<td>Surgery Unit</td>
<td>Biliary tract cancer</td>
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<td>16</td>
<td>16</td>
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<tr>
<td>18</td>
<td>60</td>
<td>m</td>
<td>Emergency surgery</td>
<td>Pancreatitis</td>
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Fig 1. (every 4 hours) glycemic measurements on the day preceding the start of treatment with NPL and parenteral nutrition.
Table 2. Mean glycemic values on days 0, 2, 3, 5 (every 4 hours) and standard deviation (SD).

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Day 0</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Overall SD</th>
<th>Days 2,3,5 SD</th>
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<td>8</td>
<td>194</td>
<td>166</td>
<td>158</td>
<td>154</td>
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<tr>
<td>12</td>
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<td>173</td>
<td>162</td>
<td>155</td>
<td>6.87</td>
<td>7.41</td>
</tr>
<tr>
<td>16</td>
<td>171</td>
<td>160</td>
<td>162</td>
<td>148</td>
<td>8.20</td>
<td>6.18</td>
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<tr>
<td>20</td>
<td>180</td>
<td>154</td>
<td>167</td>
<td>162</td>
<td>9.44</td>
<td>5.35</td>
</tr>
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<td>24</td>
<td>182</td>
<td>175</td>
<td>163</td>
<td>159</td>
<td>9.20</td>
<td>6.80</td>
</tr>
<tr>
<td>4</td>
<td>156</td>
<td>172</td>
<td>158</td>
<td>150</td>
<td>8.06</td>
<td>9.09</td>
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</table>
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, hypogenesis 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. Morbidity 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

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

References