Research Protocol

Linagliptin plus insulin for hyperglycemia immediately after renal transplantation: A comparative study

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Introduction

Hyperglycemia in hospitalized patients, defined as blood glucose equals to or greater to 140 mg/dl (7.8 mmol/L), is a common problem, since about one third of the patients have blood glucose levels above 126 mg/dl (6.99 mmol/l). Umpierrez et al, found that 26% of the admitted patients to a hospital had T2D (type 2 diabetes) and 12 % had hyperglycemia without history of diabetes (1). Other studies have reported frequencies varying from 32 % of hospitalized patients in general wards, and increasing to 40% in non-cardiac surgery, 58 % in patients with Acute Coronary Syndrome and 80% in cardiac surgery patients. The treatment goals are blood glucose between 140 to 180 mg/dl (7.77 to 9.99 mmol/l) for critically ill patients, and 110 to 140 mg/dl (6.11 to 7.77 mmol/l) in selected populations(2, 3).

In hospitalized patients, the blood glucose levels that are safer are not known, but apparently, they are narrow. General mortality rate for normoglycemic patients has been reported to be 1.7%, for previously known diabetic patients, 3.0% and for new hyperglycemic patients 16%; in patients admitted to ICU (intensive care unit), the mortality rate was 10% for normoglycemic patients, 11% for diabetic patients and 31 % for new hyperglycemic patients. The increment of death risk was 2.7-fold for diabetic patients and 18.3-fold for new hyperglycemic patients (1).

The variations in blood glucose levels (lower or higher than normal) are related to an increased mortality, longer hospitalizations and increased morbidity (infections, impaired immune response and wound healing, activation of inflammatory cytokines, pro thrombotic state, increased production of reactive oxygen species in the mitochondria), and are not limited to diabetic-known patients (2-4).

The minimal risk of death has been related to plasmatic glucose levels of 89 mg/dl (4.94 mmol/l) (range 78 -101 mg/dl or 4.33-5.6 mmol/l), glucose levels between 60 to 80 mg/dl (3.33 to 4.44 mmol/l) had an OR of 1.06, and glucose levels between 100 to 200 mg/dl (5.55 to 11.10 mml/l)

were associated with an odds ratio of 1.32 for in-hospital death. Interestingly, the relation of plasmatic glucose with mortality showed a "J" shape curve, suggesting that low or high blood glucose levels are both deleterious (5). In cardiac surgery patients and Acute Coronary Syndrome (ACS), the risk threshold begins with blood glucose levels as low as 140 mg/dl (7.77 mmol/l). Other authors mention this "J" shape curve in the relation between blood glucose levels and mortality (2, 3).

Mortality, length of in-hospital stay and acute kidney failure have been associated to hyperglycemia in different studies postoperatively (3, 6).

During acute inflammation, hyperglycemia decreases vasodilatory response and reduces the blood flow to the sites of infection (or inflammation), it also increases endothelial permeability and tissue edema, which can cause multisystem organ dysfunction (4).Hypoglycemia is one of the main limitations for the tight glycemic control. Frequency of hypoglycemia varied between 24.3 to 27.8 %, in the glucose-controlled patients, and between 72.2 to 75.6% in non-controlled patients(6).

Not only hyperglycemia causes damage, glycemic variability and hypoglycemia does too, and it seems to be worse than hyperglycemia itself.

Mean amplitude of glycemic excursions keeps and almost lineal relation (r 0.86) with the renal excretion of 8-iso prostaglandin $F_{2\alpha}$, a marker of oxidative stress (7). Hypoglycemia itself increases C-reactive protein and pro-inflammatory cytokines (TNF-α, interleukin-1β, IL-6, and interleukin-8), markers of lipid peroxidation, ROS, and leukocytosis (3).

There is an apparent paradox: hyperglycemia increases the danger of death and morbidities in hospitalized patients, but the best treatment option – insulin – can be more dangerous itself, because of the hypoglycemia risk.

The recommended treatment of hospitalized patients with hyperglycemia is a combination of insulin analogs This is accomplished using insulin analogs with slow release rate (basal insulin) and other

ones with fast or very fast release rate (prandial insulin); the so-called basal bolus insulin regimen. As general rule point of care capillary glucose determinations are performed before meals, to adjust the dose of prandial insulin (8).

The incidence of cardiovascular events in T2D patients are a set of adverse outcomes of interest; drugs used for the treatment of T2D are required to probe that do not increase the risk of cardiovascular diseases (9).

The evaluation of DPP4 (dipeptidyl peptidase-4) inhibitors has provided variable evidence. Most of the studies have proved that the use of DDP4 inhibitors is safe, regarding cardiovascular outcomes(10, 11). The odds ratio for hospitalization for heart failure (HF) in iDPP4 users were 1.00 (95% CI 0.94 to 1.07), incident HF 1.01 (95% CI 0.92 to 1.11) recurrent HF 1.02 (95% CI 0.84 to 1.22). All-cause mortality was 6% lower in iDPP4 users ($p < 0.001$). Insulin users showed an excess of risk for any type of hospital admission (19%) and death (20%) ($p<0.001$) (12).

Different studies in patients with acute coronary syndrome and high cardiovascular risk have shown a safe profile of linagliptin regarding cardiovascular and renal function (13-15).

Post-transplanted renal patients have a particularly high risk of hyperglycemia after renal transplantation (RT). Surgery procedures are related with elevation of blood glucose levels; as result of the trauma itself there is release of cytokines and stress response hormones that cause insulin resistance. In post transplanted patients, we must add the use of immunosuppressive therapy that worseness this insulin resistance effect. The incidence of hyperglycemia is common in these patients; for example, in post kidney transplanted patients the frequency reported is between 80 to 90 %. Sometimes, the patients were already diabetic previous to the transplant (but unaware); other times, they are actually new diabetes cases. Hyperglycemia in the perioperative period, independently if the patients continues with post-transplant diabetes mellitus (PTDM) or remits to

normoglycemia, has been related to increased graft rejection, infections or readmission to the hospital because of infection (16).

The recommended treatment of hyperglycemia in kidney transplanted patient is insulin analogs. There are several algorithms that had proven to be effective; but as the conditions of these patients can change rapidly (adjustment of the immunosuppressive drugs, changes in renal function or nutrition therapy), they require intensive blood glucose monitoring, effective communication among the health care team (nurses and physicians), flexible treatment algorithms, and training of the personal to understand and implement properly these algorithms. All these conditions create a very challenging environment for the adequate use of insulin analogs. The use of DPP4 inhibitors in the treatment of diabetic patients that had underwent kidney transplantation is increasing. There are, nevertheless, few studies that had assessed the efficacy and security of these drugs, in the setting of diabetic kidney transplanted patients (16).

Although they all are capable to lower glucose, they do not do so in the same proportion. In the study by Bae et al, they compared the hypoglycemic effect of three different DDP4 inhibitors (sitagliptin, vildagliptin and linagliptin) *in a population of renal transplanted diabetic patients*; it was found that the mean difference between the pre and post treatment glycated hemoglobin (HbA1c) were -0.53 for sitagliptin, -0.38 for vildagliptin and – 1.4 for linagliptin. In the same study, it was reported that the average cyclosporine blood levels in the pre and post treatment period changed +30.62 ng/mL in sitagliptin group, -24.22 ng/mL in vildagliptin group and -8.5 ng/mL in linagliptin group (17).

The goal of this work was to evaluate the effect of the combined treatment with insulin plus linagliptin in comparison with insulin alone on glucose control and hypoglycemia in post-transplanted renal patients who present hyperglycemia immediately after RT.

Material and methods

Study design and population

This was a retrospective comparative study performed in a single center between 2016 and 2018, included the data collected from 28 hospitalized post-renal transplanted patients that presented hyperglycemia (>140 mg/dl or or 7.77 mmol/l) immediately after RT; 14 patients were treated with linagliptin 5mg daily plus a basal bolus insulin scheme prescribed by the Endocrinology group at the hospital, and 14 patients treated only with basal bolus insulin scheme were randomly selected from a list of patients treated during the same period of time and by the same Endocrinology group. Linagliptin dose was 5mg daily and the basal bolus insulin regimen was started and adjusted according to the international guidelines; in general, patients received a starting insulin dose of around 0.5 U/kg/day, given half as basal insulin (NPH or Glargine) once or twice daily and half as insulin lispro divided into three equal doses before meals. Insulin dose was adjusted daily to achieve the goal of fasting glucose between 80-140 mg/dl (4.44-7.77 mmol/l) or random glucose levels below 180 mg/dl (9.99 mmol/l). Correctional insulin dose was used before each meal, depending on the glucose measurements, starting at 1 unit for each 40mg above 140 mg/dl (7.77 mmol/l) of glucose. Glucose levels were monitored at fasting and before each meal, as well as at bedtime according to standard clinical practice. Data regarding fasting and preprandial glucose levels, hypoglycemia, renal function, and immunosuppression therapy were recorded from the patient´s file during the first 5 days after RT; fasting glucose and renal function were also recorded at 1, 6 and 12 months after RT. Patients were included if they were between 18-65 years of age and presented fasting hyperglycemia (>140 mg/dl or 7.77 mmol/l) immediately after RT.

Ethical and Research committee at the Hospital approved the study protocol with the number CEI-49-18.

Fasting glucose was measured by dry chemistry with colomitetric method (Vitros 5600; Ortho Clinical Diagnostics), pre-lunch and pre-dinner glucose were measured by capillary method using and Accu-check glucometer. Hypoglycemia was defined when glucose levels were <70 mg/dl (3.88 mmol/l).

Main Outcomes were glucose levels during the first 5 days in hospital and after 6 and 12 months, insulin dose, frequency and severity of hypoglycemia, and renal function at 1, 6 and 12 months after RT.

Statistical analysis

We used unpaired t test for numerical comparisons between the groups treated with linagliptin + insulin vs insulin alone, and a paired t test for intra-group comparisons. Chi square test was used to compare proportions between the study groups. A p value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 22 (SPSS, Chicago, IL).

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