Research Protocol Covid-19H

Effect of the Combination of DPP4i and insulin in comparison to insulin on metabolic control and prognosis in hospitalized patients with SARS-CoV-2 infection

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Introduction

Hyperglycemia in hospitalized patients

Most of the cases with hospital hyperglycemia correspond to patients with type 2 diabetes (T2D), however, a significant percentage of patients without known T2D may also present hyperglycemia. This may be due to the fact that patients have a high risk of T2D, prediabetes or unknown hyperglycemia, but it is also due to the combination of other factors such as acute stress due to the patient's pathology and the different treatments used with hyperglycemic effect, in particular immunosuppressors and glucocorticoids.

In the case of patients with T2D, it is clear that the disease itself increases the risk of hospital hyperglycemia, since T2D is characterized by different pathophysiological alterations such as: insulin resistance, pancreatic beta cell dysfunction, pancreatic alpha cells dysfunction, amyloid deposits, reduction of the incretin effect, etc., which together contribute to the development of hyperglycemia[1]

Hyperglycemia in hospitalized patients has a high incidence since 30% to 40% of patients seen in the emergency services and 25% to 40% of those hospitalized in medical or surgical areas are patients with T2D. In a retrospective study carried out in a regional Mexican hospital, 69% of diabetic patients had hyperglycemia at the time of their hospitalization. Other studies have identified that 38% of hospitalized patients had hyperglycemia, where 26% of the patients knew the diagnosis of T2D and 12% of the patients did not know it[2].

Impact of hyperglycemia in the hospitalized patient

Hyperglycemia in hospitalized patients generates greater morbidity and mortality both in patients with T2D and in patients without T2D. A multicenter prospective cohort study that included 2471 patients in 6 hospitals with community-acquired pneumonia revealed that glucose concentration of more than 198 mg / dL at hospital admission was associated with higher mortality (13% vs. 9% , p = 0.03) and complications (29% vs 22%, p = 0.01) compared to those patients with a lower glucose concentration [3]. Observational studies suggest that elevated glucose levels, especially in patients without T2D, are associated with greater adverse events, higher mortality and less functional recovery in patients with stroke[4]. In patients suffering from an acute coronary syndrome, hyperglycemia in both patients with T2D and without T2D has been associated with increased morbidity and mortality[5]. Surgical patients with hyperglycemia also show an increased risk of negative results. In a case-control

study, elevated glucose levels increased the risk of postoperative mortality in elective non-cardiac and non-vascular surgery. Patients with a random preoperative glucose concentration of 110–200 mg / dL, or more than 200 mg / dL, had 1.7 and 2.1 times higher mortality, respectively, compared to those with glucose levels less than 110 mg / dL[6]. There is also a strong association between elevated glucose levels in the perioperative period with infections. The infection rate increases 2.7 times in those patients who reach a serum glucose greater than 200 mg / dL on the first postoperative day. Additionally, patients with glucose levels greater than 200 mg / dL have a 5.7 times increased risk of severe infection [7].

Several factors are involved in the development of hyperglycemia in hospitalized patients, infectious and inflammatory processes and the use of different medications, for example glucocorticoids, are associated with hyperglycemic events. Hyperglycemia can be an initial manifestation of a serious disease as a metabolic and hormonal response. As previously mentioned, the possible mechanisms by which hyperglycemia increases mortality are: changes in coagulation, alterations in endothelial function and an increase in inflammatory cytokines. Direct evidence to support the above was provided by Esposito et al., Who demonstrated that in normal subjects and people with glucose intolerance (IGT), hyperglycemia induces the production of inflammatory cytokines interleukin (IL) -6, tumor necrosis factor -α (TNF-α) and IL-18 by an oxidative mechanism[8]. Using an artificial pancreas (Biostator, Life Sciences) they induced acute hypeglycemia set at 15 mmol / L for 5 hours while blocking endogenous insulin secretion with octreotide. Inflammatory cytokines increased in response to hyperglycemia both in normal individuals and in the IGT group, but the response was greater in the latter. The cytokine response could be blocked by glutathione infusion, suggesting that the cytokine response induced by hyperglycemia occurs mediated by an oxidative mechanism. They also showed that the effects of sustained hyperglycemia could be produced by transient fluctuations in glucose levels and that this response was greater in patients with IGT. This may be relevant for people with stress hyperglycemia, as these patients may only have elevations in blood glucose. Increases in TNF-a can alter insulin receptor signaling and increase insulin resistance[8]. Thus, elevated blood glucose levels cause an inflammatory response, leading to the production of cytokines and oxygen free radical species, which can induce hyperglycemia [9]. In patients with hyperglycemia without an obvious infection or cardiovascular disease, Stentz et al. Demonstrated that there is an increase in pro-inflammatory cytokines such as IL-1ª, IL-6, IL-8 and TNF-α, and these levels decrease once the initiation of the insulin therapy and resolution of hyperglycemia[9 10 10]

SARS-CoV-2 Infection

SARR-CoV-2 infection is a highly transmissible viral infection caused by a coronavirus that uses angiotensin converting enzyme 2 (ACE2) as a receptor on the surface of host cells, and is widely distributed in the respiratory tract and mucosa intestinal. The approximate incubation period is 14 days. The main clinical symptoms are fever, cough, general malaise, among others, and up to more than 50% of patients may be asymptomatic. Other symptoms can be nausea, loss of appetite, diarrhea, and hyposmia. The diagnosis is usually made by the history of exposure, the clinical picture, and confirmation through a virus detection test by RT-PCR. It is important to note that to date there is no definitive and effective treatment for SARS-CoV-2 infection [11].

ACE2 is a transmembrane enzyme and a functional receptor of the coronavirus S1, which from angiotensin II produces vasodilator effects from angiotensin[12]. ACE2 has been upregulated in the lungs in the context of SARS-CoV-2 infection, with type II pneumocytes being the facilitators of the inflammatory response[13]. However, ACE2 is also found in other tissues, in addition to the lungs, its influence on cardiovascular function associated with SARS-CoV-2 infection has been studied in recent years[14].

Type 2 diabetes (T2D) is associated with a high risk of different types of infections[15]. Approximately 15-35% of patients hospitalized for SARS-CoV-2 present with T2D, and probably an even higher percentage may present a high risk of hyperglycemia or early disturbances in glucose metabolism, not yet identified. Different recent reports consider T2D and obesity as variables associated with a worse prognosis in patients with SARS-CoV-2 infection[16-20].

There is evidence that T2D is a poor prognostic factor in patients with SARS-CoV-2 infection, in addition to the fact that patients with T2D have a greater susceptibility to any type of infection as well as a greater risk of complications once they present an acute decompensation[21]. In the CORONADO study, carried out in France, it was found that the main factors associated with poor prognosis in patients with T2D and SARS-CoV-2 were age, BMI and a history of micro and macrovascular complications[21].

Hyperglycemia treatment in the hospitalized patient

The management of hospitalized patients with hyperglycemia can be complicated by various circumstances, such as irregular adherence to diet, concomitant use of medications that affect glucose levels, the patient's variable neurological status, and even the variability and severity

of the disease that affects glucose metabolism. All these factors have an important influence on the daily dose of insulin that should be applied.

It is recommended that all hospitalized patients with hyperglycemia be treated with an insulin regimen that adheres to the body's physiological responses to glucose levels. The stepped insulin regimen is no longer a recommended regimen, since it does not adjust to the previous administration of insulin, at mealtime or the sensitivity of the patient, in addition there is no evidence to support its safety and effectiveness[8].

For non-critical patients, programmed subcutaneous insulin schemes are the preferred one since it allows to achieve and maintain glucose levels under control, since it includes a basal, nutritional and correction regimen. The basal bolus scheme is recommended because, among other advantages, it mimics physiological patterns of endogenous insulin excretion; It consists of the use of a basal insulin applied once or twice a day supplemented with boluses of prandial insulin plus a correction dose.

Correction schemes based on premixed insulin or biphasic action have shown a higher risk of hypoglycemia compared to basal-bolus insulin schemes according to a clinical trial carried out by Bellido and Cols. Where 64% of the patients treated with premixed insulin had hypoglycemia compared to 24% of the patients in the basal bolus group ($P < 0.001$)[22].

DPP4 inhibitors

On the other hand, traditional oral hypoglycemic agents have a limited role, due to the potential adverse effects, the slow onset of action and the long duration that determine the lack of flexibility to adapt to changing requirements throughout the day and most of them traditionally tend to be avoided in the hospitalized patient[23].

However, in recent years, and with the advent of new therapies in DM2, the usefulness that some of these new drugs could have in hospitalized patients, particularly the incretins, has been partially proposed and evaluated. Two gut-derived hormones - glucagon-like peptide -1 (GLP-1), released by L cells in the distal ileum and colon, and glucose-dependent insulinotropic peptide (GIP), released by the proximal small intestine, both of which stimulate insulin secretion from the pancreas in response to food intake: they offer a new way to reduce hyperglycemia by targeting the incretin system. Although both DPP-4 inhibitors and GLP-1 receptor (RA) agonists are well tolerated, oral administration of DPP-4 inhibitors might be preferred by some patients who can take oral medications. The efficacy and safety of incretin-based therapy for hospitalized patients is something that has not yet been fully established

and its use is currently based on expert recommendations and few research studies, it is not covered by clinical guidelines, however , the potential metabolic and cardiovascular benefits make this an attractive possibility. Native GLP-1 infusion has been reported to improve left ventricular function and cardiac performance status in patients with severe heart failure[24].

Native GLP-1, as well as GLP-1 receptor (RA) agonists such as exenatide and liraglutide, exert a number of metabolic effects that are advantageous in hospitalized patients. Most small trials have been carried out with native GLP-1, with some studies using GLP-1 RA.
In general, when GLP-1 infusion is administered to patients with or without T2D, it has been shown to normalize the glycemic response after a meal or enteral nutrition similar to insulin administration, and it has been shown to reduce exogenous insulin requirements [25,26]. Similarly, the use of a GLP-1 analog, such as exenatide, has shown some usefulness for the control of hyperglycemia due to the use of corticosteroids in hospitalized patients[27].
Dipeptidyl peptidase type 4, DPP4, is an enzyme found on the cell surface that interacts with different peptide hormones in the regulation of the immune response[28,29]. One of its main known effects is the inactivation of endogenous incretins (GLP-1 and GIP, and others not known), thus increasing the half-life of endogenous GLP-1, and thus stimulating insulin secretion by pancreatic beta cells and by reducing glucagon secretion by pancreatic alpha cells, effects for which it is used in patients with T2D[30]. Studies carried out by our group, in our hospital, have shown the usefulness of DPP4 (linagliptin) inhibitors both in patients with prediabetes to prevent and reduce the risk of developing T2D by improving the function of pancreatic beta cells[31], as well as in patients with hospital hyperglycemia after kidney transplantation when combined with basal insulin and reducing its requirements and the severity of hypoglycemia, as well as increasing the response and metabolic control[24]. Besides that, DPP4 has been associated with inflammation and its soluble levels have been reported both reduced and elevated in different inflammatory processes [32-34].

It is important to mention that all DPP-IV inhibitors are reversible competitive inhibitors and it is difficult to compare their effects when analyzing individual studies since the experimental conditions may be different; However, there is a study in which the inhibitors were compared under identical conditions showing similar efficacy (maximum effect) to inhibit DPP-IV in vitro, although there were differences in terms of potency, the most potent being linagliptin [35].

Regarding its half-life, vildagliptin and saxagliptin [36] have shorter half-lifes, on the other hand, linagliptin [37] and sitagliptin [38] have a longer duration of their effect [38] [37]

The selectivity of the different DPP-IV inhibitors for this enzyme has been evaluated in in vitro studies and it has been reported that both linagliptin[35] and sitagliptin[39] are the ones with the

highest selectivity for the DPP-IV enzyme; linagliptin has a selectivity of 10,000 for DPP-IV than for DPP-8/9 compared to sitagliptin which is 5550; This is important because the inhibition of these two DPP-8/9 enzymes is what has theoretically been thought to be associated with side effects of inhibition of lymphocyte activity, although this effect has not been observed in the clinic since, since these 2 enzymes are found intracellularly [40-42]. On the other hand, linagliptin only has lower selectivity over the fibroblast activation protein α (FAPα), which is a protein that is not found in adult tissue, so the implications of this data are even less, since the inhibitors of the DPP-IV are only indicated in adults [43].

Sitagliptin, vildagliptin and saxagliptin are eliminated in more than 80% via the kidney, whereas linagliptin is eliminated in more than 80% via the bile, so it can be used in patients with any degree of renal failure without the need to adjust the dose. and without losing the pharmacological effect.

Regarding the clinical efficacy and the capacity of the different DPP-IV inhibitors to reduce HbA1c, fasting glucose and postprandial glucose, various meta-analyzes and clinical studies have shown similar efficacy, achieving a reduction in HbA1c of between 0.5 - 1.0% (≈0.8%), with greater reductions when baseline values are higher [40-42,44,45].

Side effects and safety

To date, no higher rate of side effects have been found with DPP-IV inhibitors compared to control groups, and likewise, no differences in side effects have been reported between the various DPP-IV inhibitors [40,41,44,45]; In addition, its safety in terms of risk of pancreatitis and pancreatic cancer has recently been validated by the FDA and the European Medicines Agency [46].

Linagliptin

The mechanism of action of linagliptin consists in inhibiting the DPP-IV enzyme (dipeptidyl peptidase type IV); This enzyme (DPP-IV) has the biological effect of inactivating the glucagon-like peptide 1 (GLP-1), so when it is inhibited by linagliptin this favors endogenous GLP-1 levels to rise up to 3.2 times per above the previous values (which are reduced in patients with type 2 diabetes mellitus, which partly explains that these patients have a reduction in the incretin effect), which conditions the biological effects of GLP-1 as stimulation of the insulin secretion by pancreatic beta cells and inhibition of glucagon secretion by pancreatic alpha cells. This effect on the stimulation of insulin secretion is totally dependent

on glucose levels, so it does not cause hypoglycemia. Linagliptin has a half-life of 12 hrs so it can be used every 12 or 24 hrs, it is eliminated by the bile duct in more than 70% so it can be used in patients with nephropathy without the need to adjust the dose, it offers a power to achieve a sustained inhibition of more than 90% in DPP-IV for 24 hrs and is highly selective for inhibiting DPP-IV compared to other enzymes such as DPP-8 and DPP-9. Linagliptin is indicated in the treatment of patients with uncontrolled type 2 diabetes mellitus, which does not meet the control goals such as: Hb glycosylated less than 7%, fasting glucose less than 110mg / dl and postprandial glucose less than 140mg / dl. It can be used as therapy in combination with metformin, sulfonylureas, thiazolidinediones, and insulins, either as double or triple therapies. Recent studies have documented the renal and cardiovascular safety of linagliptin in patients with T2D [47,48].

DPP4 has also been documented to function as a receptor for coronavirus[49], and some studies in animal models have shown that by inhibiting DPP4, infection by coronavirus of the MERS-CoV type is reduced, and mice transgenes for DPP4 develop lethal infection by MERS-CoV[50-53]. Recent models from in vitro studies suggest that DPP4 is a SARS-CoV co-receptor[54], and in different studies a higher expression of DPP4 has been found in different tissues, even higher than the expression in different tissues of ACE2[55].

Experimental studies have documented that the use of some DPP4 inhibitors reduce the inflammatory response in different clinical settings [56,57].

DPP4 inhibitors improve metabolic control by increasing prandial endogenous insulin secretion and inhibiting glucagon secretion by reducing postprandial blood glucose peaks; the low risk of hypoglycemia and good tolerability make these drugs attractive for use in hospitalized patients. Furthermore, different studies have shown an anti-inflammatory effect of IDPP4 in different models of T2D [58,59], although in a case-control study it was not documented that exposure to DPP4 inhibitors had any role in preventing or reducing the risk of SARS-CoV-2 infection[60].

Different studies have been carried out comparing the use of different treatment regimens based on combinations with oral treatment and insulin. In a randomized, multicenter, prospective, open-label, non-inferiority clinical trial (Sita-Hospital) at five hospitals in the US, they enrolled patients between the ages of 18 and 80 years with type 2 diabetes and random blood glucose of 7.8-22.2 mmol / L who were being treated with diet or oral antidiabetics or had a total daily insulin dose of 0.6 units per kg or less, admitted to general medicine and surgery services. The trial met the non-inferiority threshold for the primary endpoint because there was no significant difference between the groups in mean daily blood glucose

concentrations. The study concludes that treatment with sitagliptin plus basal insulin is as effective and safe as a convenient alternative to the labor-intensive basal-bolus insulin regimen for the management of hyperglycemia in patients with type 2 diabetes admitted to general medicine and services. of hospital surgery in the non-intensive care setting[61]. In another study Umpierrez et al. Found that the total daily insulin dose and the number of insulin injections were significantly lower in the sitagliptin groups compared to the basal bolus group (both P, 0.001). There were no differences in the length of hospital stay (p = 0.78) or in the number of hypoglycemic episodes between the groups (p = 0.86) [62].

Considering all this together, The SARS-CoV-2 infection pandemic has placed great demands on health systems and has further highlighted the high impact of chronic degenerative diseases, particularly type 2 diabetes. In Mexico, a number of Increasing cases of SARS-CoV-2 infection and a large percentage of these patients have type 2 diabetes, leading to acute decompensation with hyperglycemia, hospitalization and a high risk of fatal complications. Another factor that also contributes to the prognosis in patients with type 2 diabetes is glycemic lack of control and glycemic variability, which is why it is extremely important to achieve adequate metabolic control with the minimum risk of hypoglycemia. The administration of insulin is the classic way to control hyperglycemia in hospitalized patients, however, the use of oral drugs as adjunct therapy to insulin is increasingly being proposed in order to reduce the risk of hypoglycemia, glycemic variability and metabolic lack of control. In our hospital we have carried out studies in this regard, although retrospective, where we have observed that the combination of DPP4 inhibitors with insulin provides better metabolic control and lower risk of hypoglycemia in hospitalized patients with hyperglycemia and kidney transplantation. In addition, there are several studies that compare the combination of drugs based on incretins and insulin with regimens of insulin alone, where they seem to find benefits such as the requirements and doses of insulin administered, decrease in the frequency of injections, improvement of ventricular function in infarcted patients, and decreased fluctuations in measured blood glucose levels, and theoretically, lower risk of hypoglycemia. Furthermore, biologically DPP4 has been linked to the regulation of the immune system and reduction of the inflammatory response in certain types of viral infections, in animal models and in vitro studies, the role that DPP4 inhibition plays on is not known to date. the prognosis of patients with SARS-CoV-2 infection. On the other hand, there are no studies performed with this type of therapy in patients hospitalized for SARS-CoV-2, an in-hospital population with difficult glycemic control due to systemic inflammatory response and the use of different drugs with hyperglycemic potential. The decision to use linagliptin as a DPP4 inhibitor is because it is the only one that does not have a renal elimination and therefore does not require dose adjustment

in patients with kidney damage. Searching for treatment alternatives that allow controlling hyperglycemia in this type of patients could contribute to improving the prognosis in the short and medium term, a lower risk of hypoglycemia, not prolonging their hospital stay or presenting concomitant infections, and therefore to better survival.

RESEARCH QUESTION

¿ Is here a difference in glycemic control and prognosis in patients hospitalized for SARS-CoV-2 and hyperglycemia treated with the combination of DPP4 inhibitor + insulin compared to those treated with insulin alone?

GOALS

General: To assess the effect of the combination of DPP4 inhibitor + insulin compared to insulin alone on glycemic control and prognosis in patients hospitalized for infection with SARS-CoV-2 and hyperglycemia

Specific:

-Identify patients with SARS-CoV-2 infection and hyperglycemia who meet selection criteria for the present study

-To evaluate the effect of the combination of DPP4 inhibitor + insulin on glycemic control and prognosis in hospitalized patients with SARS-CoV-2 and hyperglycemia

- To evaluate the effect of an insulin regimen on glycemic control and prognosis in hospitalized patients with SARS-CoV-2 and hyperglycemia

-Compare glucose levels and prognosis between the treatment groups

HYPOTHESIS

ALTERNATE HYPOTHESIS: There is a difference in glycemic control and prognosis in patients hospitalized for SARS-CoV-2 and hyperglycemia treated with the combination of DPP4 inhibitor + insulin in comparison to those treated with insulin alone.

NULL HYPOTHESIS: There is not difference in glycemic control and prognosis of patients hospitalized for SARS-CoV-2 and hyperglycemia treated with the combination of DPP4 inhibitor + insulin in comparison to those treated with insulin alone.

STUDY DESIGN

Single center parallel randomized clinical trial

Design: Randomized clinical trial. The randomization will be carried out by means of an electronic random number system and will be by blocks, to guarantee an equal number of participants in both groups during the study and will be performed by a physician not involved in the study. Assignment to treatments group will be blinded for the Physicians who are providing the patient`s care, researchers and personal who collect and analyze the data and outcome variables.

Study universe: Hospitalized patients with SARS-CoV-2 infection and hyperglycemia.

Study population: Hospitalized patients with SARS-CoV-2 infection and hyperglycemia in the HRAEB.

Type of sampling: Non-probabilistic of consecutive cases

Sample size: The sample size was calculated based on the formula to compare means between two groups, and using data from the previous study carried out in hospitalized kidney transplant patients in which it was observed that the linagliptin + insulin group had a final glucose level of 135 ± 14 mg / dl compared to the insulin-only group that had a glucose level of 155 ± 19 mg / dl24, considering a two-sided hypothesis, an alpha value of 0.05 and a study power of 80% (beta 0.20), the minimum sample size required per group is 17 patients per group, which including 20% expected losses, rises to 20 patients per group.

SELECTION CRITERIA

Inclusion criteria

Patient with confirmed SARS-CoV-2 infection by RT-PCR

Patients with or without T2D with a plasma glucose between 140 mg / dl and 400 mg / dl, who require hypoglycemic treatment.

Patients with tolerance to take pills orally

Patients of both sexes, older than 18 years of age

Patients who, in case of having previous treatment with insulin, this is in low doses (<or = 0.4 U / kg) before their admission.

Patients with any hypoglycemic treatment prior to hospitalization

Patients who have signed their informed consent

Hospitalized patients at the HRAEB

Exclusion criteria

Patients whose mental condition makes it impossible for them to give their informed consent.

Patients with assisted mechanical ventilation

Pregnancy

General procedure

HRAEB hospitalized patients with SARS-CoV-2 infection and hyperglycemia who meet the inclusion criteria will be invited to participate in the study. Once the patient meets the inclusion criteria and agrees to participate, they will be asked to sign an informed consent, in which the characteristics of the study, the risks and benefits will be explained. Subsequently, a sheet will be filled out with the identification and clinical history of the patient. Then, basal levels of glucose, lipids, inflammatory markers and HbA1c will be quantified by standard methods.

Subsequently, the patients will be randomized, within two treatment regimens: i) basal bolus insulin scheme, and ii) linagliptin + basal bolus insulin. Patients treated with linagliptin and basal insulin will receive an initial total daily dose of 0.25 U / Kg / d of insulin glargine, except for those patients older than or equal to 70 years of age and / or serum creatinine greater than or equal to 2 mg / day. dl, who will receive 0.15 U / Kg / d plus a daily dose of 5mg of linagliptin orally before breakfast. Patients treated with a basal bolus insulin scheme will start with a total insulin dose of 0.5 U / kg divided into 50% insulin glargine every 24 hours at 10-11pm and 50% insulin lispro divided into three doses, one third 15 minutes before each meal. In patients

older than or equal to 70 years of age or with a serum creatinine greater than or equal to 2 mg / dl, the total insulin dose will be reduced to 0.3 U / Kg. The insulin dose will be adjusted daily according to the following scheme:

The correction factor will be calculated with the following formula:

Correction factor = 1500 / total daily insulin dose.

Total daily insulin dose = IU Glargine + IU Lispro

Where one way to adjust preprandial glucose is to use the 1500 rule.

This rule is used to determine the reduction in blood glucose level for each unit of insulin that is administered. It is used when the glucose level is above the established goals, it consists of dividing 1500 by the total insulin dose (TDD), the result obtained will be the correction factor that will refer to the effect that a unit of insulin will have on the glucose, thus, if a patient who uses a total daily dose of insulin of 50 IU has a preprandial glucose of 210 mg / dl and our goal is 130 mg / dl we can apply the rule of 1500 where we will divide 1500/50 giving by As a result, our correction factor would be 30, this refers to the fact that one unit of insulin will reduce 30mg / dl of glucose in this patient, thus applying 2IU more than the base dose to reach our goal of 130 mg / dl.

The metabolic goals are:

• Fasting and preprandial blood glucose between 100-140 mg / dl

• Postprandial capillary glucose less than 180mg / dl

After starting the scheme, the capillary blood glucose measurement will continue before and after each meal, at 23:00 and 03:00 hrs. In addition, capillary blood glucose can be measured at any time that the patient experiences symptoms of hypoglycemia or as required by the treating physician. This will be recorded on a data capture sheet each day of the hospital stay.

Blood samples will be taken for glucose measurement by clinical chemistry every third day, and inflammation markers such as CRP, IL-6, TNFa, fibrinogen will be measured at the beginning and every 5 days, these by chemiluminescence. The lipid profile will only be measured initially by dry chemistry. All these studies are part of the evaluations that patients have during their hospital stay.

VARIABLES

1) Group of treatment

to. Type of variable: Independent

b. Measurement level: Dichotomous nominal

c. Unit of measurement: Group A (patients with hyperglycemia and SARS-CoV-2 infection receiving treatment with Linagliptin + insulin), and Group B (patients with hyperglycemia and SARS-CoV-2 infection receiving treatment with insulin only).

d. Conceptual definition: Treatment that is started to control hyperglycemia in hospitalized patients

and. Operational definition: Group A will be those patients with hyperglycemia and SARS-CoV-2 infection who will receive treatment based on Linagliptin 5mg every 24 h + insulin for at least 48 hrs and who have follow-up of blood glucose and subsequent blood glucose tests for at least less 5 days. Group B will be those patients with hyperglycemia and SARS-CoV-2 infection who will receive insulin-based treatment and who have follow-up of blood glucose and subsequent blood glucose tests for at least 5 days.

2) Fasting glucose

a) Type of variable: Dependent

b) Measurement level: Quantitative

c) Unit of measurement: mg / dL

d) Conceptual definition: Measurement performed while fasting to record glucose levels by capillary glucometry.

e) Operational definition: It will be the glucometry recorded in fasting prior to the first morning meal using capillary glucometry with Accu-Chek device and / or by clinical chemistry

3) Postprandial glucose

to. Type of variable: Dependent

b. Measurement level: Quantitative

c. Unit of measurement: mg / dl

d. Conceptual definition: Calipar glucose measurement that reflects the absorption and muscular consumption of glucose after food intake

and. Operational definition: Glucose measurement 2 hours after food intake, using an Accu-Check glucometer or whatever is available in the service. It will be held post-breakfast, post-lunch and post-dinner.

4) Glycemic control

a) Type of variable: Dependent

b) Measurement level: Qualitative nominal dichotomous

c) Unit of measurement: Yes or No

d) Conceptual definition: fasting glycemic levels between 110 and 140 mg / dL in preprandial and fasting blood glucose tests, and less than 180 mg / dl in postprandial blood glucose tests.

e) Operational definition: It will be considered as glycemic control when the fasting capillary glucose level is less than 140 mg / dl and the postprandial level is less than 180 mg / dl.

5) Time in which glycemic control is reached

a) Type of variable: Dependent

b) Measurement level: Discrete quantitative

c) Unit of measurement: Days it takes to achieve metabolic control in the study groups.

d) Conceptual definition: Number of days in which patients achieve glycemic control from the beginning of the intervention in the study groups.

e) Operational definition: Number of days in which patients reach preprandial capillary blood glucose levels less than 140 mg / dl and postprandial levels less than 180 mg / dl.

6) Insulin dose:

a) Type of variable: Dependent

b) Measurement level: Discrete quantitative

c) Unit of measurement: Units of insulin used per day in groups: A (patients with post-renal transplant hyperglycemia receiving treatment with Linagliptin + insulin), and Group B (patients with post-renal transplant hyperglycemia receiving treatment only with insulin).

d) Conceptual definition: The total amount of IU used per day in the two groups of patients.

e) Operational definition: The total IU of insulin used per day in the two groups will be reviewed.

7) Prognosis

to. Type of variable: Dependent

b. Measurement level: Dichotomous nominal

c. Unit of measurement: Good or bad

d. Conceptual definition: Prognosis of the patients included in the study groups, which can be modified by the course of the underlying disease, and which can include from recovery with discharge home, to in-hospital complications and death.

Operational definition: Prognosis is **Good** when the patient has recovered and is discharged home due to improvement without needing mechanical ventilation, and **Poor** when the patient requires assisted mechanical ventilation and / or when the patient dies, which will be verified by a death certificate.

8) Frequency and severity of hypoglycemia

a) Type of variable: Dependent

b) Measurement level: Dichotomous nominal

c) Unit of measurement: Number and severity of hypoglycemia recorded in the time that the in-hospital treatment lasted.

d) Conceptual definition: Serum glucose levels <70 mg / dL

e) Operational definition: Record of blood glucose levels recorded by capillary blood glucose testing that were less than <70 mg / dL.

Other variables: Age, sex, weight, BMI, HbA1c, lipid profile, inflammation markers (CRP, IL6, fibrinogen, TNFa), APACHE, SOFA.

STATISTICAL ANALYSIS

Descriptive statistics will be used for the general presentation of the data; The comparison of numerical variables between the study groups before and after the intervention will be carried out using the Student's t test for independent groups, the comparisons in each initial-final study group will be carried out using the paired t test, as well as the ANOVA test for repeated measurements. Likewise, a risk analysis (RR, RRA, RRR, NNT) and Kaplan-Maier curves will be carried out to analyze the probability of glycemic control and the presence of complications and patient survival, and a model of analysis of Cox risk. The qualitative variables will be compared using the Chi square test. A statistically significant difference will be considered when the p value is less than 0.05. Statistical analysis will be performed with SPSS version 21 and Stata version 15.1 software.

ETHICAL ASPECTS

This study has been approved by the Research Ethics and Research Committees of the Hospital Regional de Alta Especialidad del Bajío with the following numbers CEI-22-2020 and CI-HRAEB-42-2020, and will be carried out in adherence to the ethical standards, the Regulation of the General Health Law on Research for the health and the Declaration of Helsinki of the World Medical Association of the 64th General Assembly, Fortaleza, Brazil in 2013 and current international codes and standards of good clinical research practices. Special attention will be paid to taking care of the confidentiality of patient information. Patients will be asked to sign an informed consent letter, and a confidentiality letter will also be signed by the authors of this Research Project.

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