"Physiological" insulin scheme vs "Traditional" scheme for glycemic control in non-critical hospitalized patients with Type 2 Diabetes Mellitus: Controlled Clinical Trial

Registration number: NCT03350984

Date: 02/08/2019

MATERIAL AND METHOD

TYPE OF STUDY:

- Clinical controlled trial, randomized, not blinded, comparative between 2 groups.

WORKING UNIVERSE

- Patients with diabetes mellitus type 2.

SAMPLING FRAME

- Hospitalized patients in the medical and surgical services of the hospital: internal medicine, traumatology and orthopedics and general surgery of the General Hospital of León not critical with diabetes mellitus type 2.

SAMPLE SIZE

- It was determined a minimal sample size of 33 patients per group plus 7 extra patients in each group to compensate possible losses, which gave a total of 40 per group. The sample size was determined by the formula: n=(Zα/2+Zβ)2 * (p1(1-p1)+p2(1-p2)) / (p1-p2)2.(36) It was considered the probability of making a mistake type 1 (α) of 0.05, a statistical potential (1-β) of 0.80 and a difference of 25% in the rate of hypoglycemia in reference with the one reported in the meta-analysis of Christensen MB el al(27), for both treatments in a bicaudal way in the distribution curve.

SAMPLING TYPE

- Randomized systematic sampling. The assignment to the treatment schemes was made using a randomized numbered table generated by a computer. If more of one patient arrived to the hospital at the same time, they were randomized in order of the service they arrived: Internal medicine (IM): 1st, Traumatology and orthopedics (TyO): 2nd and General surgery(GS): 3rd, and in base of the number of bed from lower to higher.

INCLUSION CRITERIA

- Patients older than 18 years old, with diagnosis of diabetes type 2 with central fasting glucose before randomization between 140mg/dl and 400mg/dl.
- Patients that were diagnosed at admission with DM2 with HBA1>6.5% and fasting glucose >126mg/dl (isolated hyperglycemia >200mg/dl was not considered as a diagnostic parameter because of the stress conditions, metabolic response to the base pathology or steroid exposition that can alter the glycemia values in hospitalized patients).
- Patients in not critical state.
- Patients with a diet for diabetic patient per oral administration at least 3 times

daily.

EXCLUSION CRITERIA

- Parenteral nutrition and continuous enteral nutrition by nasogastric tube.
- Chronic kidney disease with a glomerular filtration rate <15mg/dl or in renal replacement therapy.
- Hyperosmolar state or diabetic ketoacidosis.
- Diabetes mellitus type 1
- Hyperglycemia due to stress (negative history of DM2, hyperglycemia and HbA1C<6.4)
- - Parenteral nutrition and continuous enteral nutrition by nasogastric tube.
- - Chronic kidney disease with a glomerular filtration rate <15mg / dl or in renal replacement therapy.
- - Hyperosmolar state or diabetic ketoacidosis.
- - Diabetes mellitus type 1.
- - Hyperglycemia due to stress (negative history of DM2, hyperglycemia and HbA1 <6.4)
- - Treatment with any steroid equivalent to more than 10mg of prednisone.
- - Pregnancy.
- - CHILD PUGH C hepatic failure
- - Acute pancreatitis.
- - Sepsis, septic shock or multiple organ failure.

ELIMINATION CRITERIA

- Patient who is discharged by voluntary discharge.
- Patient who, due to their clinical condition that causes aggression (frontal syndrome, psychotic state, alcohol withdrawal syndrome, etc.), prevents the application of their treatment.

PROCEDURE

- Patient selection:

Once the protocol was approved by the HGL committee, the selection of patients was initiated; those who met the inclusion and exclusion criteria were invited to participate in the study with prior informed consent (Annex 2). Upon entry to the floor of internal medicine, general surgery and trauma, a record sheet was filled out with the data, which included weight, height, central glucose levels and glycosylated hemoglobin. Patients that were not diagnosed but with HbA1> 6.5 were also included in the study.

- Assignment of the groups:

Patients with diabetes or with HbA1> 6.5% were assigned to the insulin scheme

according to a systematic randomization which was done by means of a table of random numbers generated by a computer, as they were entering the different floors of internal medicine, general surgery or traumatology. The assigned scheme was placed in the internal part of the folders of indications and vital signs of each patient. The emblem of "Patient in protocol" highlighted with a striking color was the identifier of patients in protocol.

-Patient monitorization

At least one sample of central glucose and one HbA1c determination were taken at the time of admission to the protocol. A fasting blood glucose was taken every day, 2 hours after breakfast, before lunch, before dinner and 2 hours after dinner, as well as capillary blood glucose at midnight at 3 am. The data obtained were recorded on the nursing working sheet.

- About the control of diet and calories for patients

Upon entering the protocol, a standardized diet for patient with diabetes was assigned to each patient with a caloric intake of 1600 to 2000 kcal depending on the requirements for body weight, calculated by the nutrition staff. The distribution was 50% of carbohydrates, 30% of lipids and 20% of proteins. In those patients who continued with hyperglycemia and didn't have control with a standardized diabetic diet, an individualized diet was performed, for which an energy requirement calculation was made 25-30 kcal/kg and in patients with obesity 20 kcal/kg. The distribution of carbohydrates 45-55% and lipids 25-35%, proteins 15-25%.

A food ration was provided at breakfast between 8 - 9hr, another at 14 - 15hr and another at approximately 20-21hr.

For patients who showed a tendency to hypoglycemia, in addition to the insulin adjustment, snack foods were indicated by the nutrition service. The assistance of family members and nurses was requested to ensure that the ration of their food was finished. In those patients who presented episodes of hypoglycemia associated with not finishing their food, designated insulin scheme was suspended.

-Protocol of insulin treatment and management of hypoglycemia:

1. Schematic "Physiological"

A. Patients previously treated with insulin or patients who were not treated on an outpatient basis with insulin (oral diet or hypoglycemic agents) or first diagnosis of DM2: Suspend the dose of insulin applied and stop the oral antidiabetic drugs on admission and replace them with insulin, Initiating the total daily dose: When the basal glucose is between 140 and 200 mg / dl: 0.4 IU/kg/day and between 201 and

400 mg/dl: 0.5 IU/kg/day. When the patient is susceptible to hypoglycemia events (localized infection, glomerular filtration rate of 16-30 ml/min/m2, age greater than 70 years), the dose of 0.35 IU/kg/day may be initiated at the endocrinologist's consideration.
- 50% of the total insulin dose with Glargine and the other 50% with Lispro insulin fractionated according to the number of foods.
- Glargine is administered once a day, at 8 pm.
- Lispro is administered in three divided doses proportionally immediately before each meal.
- To prevent hypoglycemia, if a subject cannot eat, skip the Lispro insulin dose of that food.

B. Insulin adjustment:
- If fasting capillary glucose is <140 mg/dl in the absence of hypoglycemia: no change.
- If fasting capillary glucose is between 140 and 180 mg/dl: the total insulin dose increases by 10%.
- If fasting capillary glucose is>180 mg/dl: increase the total insulin dose by 20%.
- If fasting capillary glucose is <70mg/dl, decrease the daily dose of total insulin by 20%.

C. Supplemental Insulin: Administer insulin Lispro according to the protocol "Complementary scheme". The scheduled insulin dose during the meal hour was supplemented with insulin lispro if basal glucose was higher than 180mg/dl by the "complementary scheme" protocol (Annex 1). If fasting or postprandial capillary glucose persists >180mg/day despite the previously assigned scheme:
- If a patient can eat all or most of their meals, administer supplemental insulin Lispro following the "usual" column.
- If a patient cannot eat, has a soft tissue infection, is >70 years old or has a glomerular filtration rate of 15-30ml/min, administer supplemental insulin Lispro following the "insulin-sensitive" column.
- If the capillary glucose is persistently >180 mg/dl in the absence of hypoglycemia, increase the insulin scale from the "sensitive" to "usual" column or from the "usual" column to the "resistant" column.

2. Traditional Scheme:

A. Patients previously treated with insulin or patients who were not treated on an outpatient basis with insulin (oral diet or hypoglycemic agents) or first diagnosis of DM2: Suspend the insulin dose applied and stop the oral antidiabetic drugs on admission and replace them with insulin, initiating Total daily dose: If basal glucose

is between 140 and 200 mg/dl: 0.4 IU/kg/day. If basal glucose is between 201 and 400 mg/dl: 0.5 IU/kg/day. When the patient is susceptible to hypoglycemia (localized infection, glomerular filtration rate of 16-30 ml/min/m2, age greater than 70 years), the dose of 0.35 IU/kg/day may be initiated at the endocrinologist's discretion.
- 2/3 parts of the calculated dose with NPH Insulin at 8 a.m. and 1/3 part of the dose at 8 p.m., is always administered at the same time.
- In order to prevent hypoglycemia, if a subject cannot eat, suspend the dose of NPH insulin.

B. Insulin adjustment:
- If fasting capillary glucose is <140 mg/dl in the absence of hypoglycemia: no change.
- If fasting capillary glucose is between 140 and 180 mg/dl: the total insulin dose increases by 10%.
- If fasting capillary glucose is>180 mg/dl: increase the total insulin dose by 20%.
- If fasting capillary glucose is <70mg/dl, decrease the daily dose of total insulin by 20%.
C. Supplemental Insulin: Administer supplemental insulin lispro in addition to NPH insulin programmed for baseline glucose greater than 180 mg/dL using a supplemental insulin protocol (Annex 1). If fasting or postprandial capillary glucose persists>180mg/day despite the previously assigned scheme:
- If a patient can eat all or most of their meals, administer supplemental insulin Lispro following the "usual" column.
- If a patient cannot eat, is>70 years old, soft tissue infection or has a glomerular filtration rate of 16-30ml/min, administer supplemental insulin Lispro following the "insulin-sensitive" column.
- If the capillary glucose is persistently>180 mg/dl in the absence of hypoglycemia, increase the insulin scale from the "sensitive“ to "usual" column or from the "usual “column to the "resistant“ column.

3. Management of Hypoglycemia

If a capillary glucose measurement of the patient has <70mg/dl, either by hourly capillary glucose or by the presence of clinical symptoms (sweating, chills, dizziness, nausea, hunger, blurred vision, numbness, paresthesia of the lips or tongue) and is alert, provide oral feeding equivalent to 15 grams of carbohydrates (1 serving of food or 1-2 tablespoons of sugar) or 30ml of 50% glucose solution.
If the patient presents altered state of consciousness (drowsiness, confusion, or stupor) or does not tolerate the oral route, apply 30ml of 50% glucose solution (15 grams of carbohydrates) and 15 minutes later take a new capillary blood glucose measurement. If glucose levels continue <70mg / dl, a new dose of 15g of

carbohydrate is applied every 15 minutes until glucose >70mg/dl is reached.

If during the study patients present more than 1 event of hypoglycemia after adjustment with a 20% decrease in insulin dose after a first event, in the absence of fasting, suspend the insulin regimen. Only restart insulin scheme in the case of disappearance of the hypoglycemia risk factor.

STATISTICAL ANALYSIS

The descriptive statistical analysis was carried out in the following way: for the qualitative variables proportions and percentage rates (%) were reported; for the quantitative variables, mean and standard deviation or median and interquartile range (Q1 to Q3) were reported according to the distribution of the data. The normality of the distribution was determined by the Kolmogorov-Smirnov test.

The univariate inferential analysis was performed using the chi-square test or Fisher's exact test for the qualitative variables, according to the distribution of the expected values in the contingency table. For the numerical variables, the t test was used for two independent samples or its non-parametric version, according to the nature of the distribution of the numerical data. A p value <0.05 was considered significant.

For the analysis of the treatment, the risk analysis model will be used with the calculation of the RR, RAR, RRR, its 95% Confidence Interval (95% CI) and the NNT was determined for the traditional scheme, once the data were concluded. The analysis was considered by protocol and by intention to treat.

RESULTS

PATIENTS OF THE STUDY

A total of 111 hospitalized DM2 patients not critical to the study were evaluated. Of these, 35 did not meet the inclusion criteria and the 76 included participants were randomized into two groups. The recruitment of patients began on November 15, 2017 and ended on June 1, 2018. The "physiological" insulin group with 37 participants and the traditional group with 39 participants. Within the "physiological" group, 1 patient was eliminated before initiating the insulin regimen, presenting acute abdomen and requiring intensive therapy. Therefore, 36 patients in the "physiological" group and 39 patients in the traditional group began treatment, who entered the analysis for intention to treat. From the physiological group 6 patients did not conclude the treatment by discharge before the control and 2 patients due to poor adherence to the treatment. In the traditional group, 5 patients withdrew before the control, 1 patient due to poor adherence to treatment, 1 patient died before the control, and 1 patient was suspended due to critical condition. At the end of the study, 28 patients in the "physiological" group and 31 patients in the traditional group were completed in the analysis per protocol. In 20 (71.4%) patients in the first group and in 30 (96.8%) patients in the second group, treatment was completed until discharge.

POPULATION CHARACTERISTICS

Of the total patients analyzed for intention to treat, 34 (45.3%) patients were men and 41 (54.7%) women. According to the place of hospitalization, 18 (24%) were in the internal medicine service, 29 (38.7%) in traumatology and orthopedics and 28 (37.3%) in general surgery. The mean age of the patients was 57.83 ± 13 years. The average body mass index was 26 ± 5.1 kg / m2. The mean random glucose at admission was 230.5 ± 70.2 mg / dL, the glycosylated hemoglobin level was 8.3 ± 2.3%, and the serum creatinine was 1 ± 0.5 mg / dL. The treatment before admission was with oral hypoglycemic agents in 25 (33.3%) patients, with insulin in 25 (33.3%) patients, the combination of oral hypoglycemic agents and insulin in 12 (16%) patients and 13 (17.3%) patients. they received treatment or were diagnosed at the time of admission. The average dose of insulin administered was 29.6 ± 11.6 IU and the number of days of hospital stay was 9.3 ± 5 days. The reasons for admission to the hospital were: abscesses and soft tissue infection, hip fracture, diabetic foot, other fractures, cancer, heart disease, gastrointestinal bleeding, acute cholecystitis, stage IV chronic kidney disease, pneumonia, gonarthrosis, pathway infection urinary tract, intoxications, meningitis, alveolar obesity-hypoventilation syndrome, peripheral thrombosis and obstructive uropathy.

EFFECTIVENESS RESULTS

When evaluating efficacy, by protocol, the following was observed: The fasting glucose average in the "physiological" group was 130.3 ± 20.9 mg / dl, while in the traditional group it was 126 ± 22 mg / dl (p = 0.114); the average postprandial glucose in the physiological group was 150.8 ± 22.8 mg / dl and in the traditional group it was 149.4 ± 28.1 mg / dl (p = 0.833). The average morning glucose in the first group was 130.9 ± 18.3 mg / dl and 125.9 ± 26.7 mg / dl in the second group (p = 0.081).

In the analysis by intent to treat in the same way control was achieved in goals in both groups. The average fasting glucose in the "physiological" group was 135 ± 22.6 mg / dl, while in the traditional group it was 129.6 ± 23.6 mg / dl (p = 0.114); the average postprandial glucose in the physiological group was 156.2 ± 27.2 mg / dl and in the traditional group it was 155.4 ± 29 mg / dl (p = 0.902). The average morning glucose in the first group was 136.2 ± 21.2 mg / dl and 127.4 ± 26.6 mg / dl in the second group (p = 0.081).

The number of days to reach control during the hospital stay statistically were not different between groups (by protocol 4.9 ± 2.2 days vs 4.7 ± 2.4 days, p = 0.553, by intention to treat 4.9 ± 2.1 days vs 4.7 ± 2.3 days, p = 0.445).

SAFETY RESULTS

Safety was evaluated with episodes of hypoglycemia and complications associated with diabetes. In the "physiological" group it was observed that 15 (41.6%) patients had at least one event of hypoglycemia during their entire stay; On the other hand, in the traditional group 15 (38.4%) presented at least one event of hypoglycemia (per protocol, RR: 1.11, 95% CI: 0.62 to 1.97, p = 0.729; intention to treat, RR = 1.08, 95% CI: 0.62 to 1.89, p = 0.777). The presence of more than 2 hypoglycemic events during their hospitalization was observed in 8 (22.2%) patients of the "physiological" group and in 2 (5.1%) patients of the traditional group (per protocol, RR = 7.75, 95% CI: 1.02 a 59.13, p = 0.021; by intention to treat, RR: 4.33, 95% CI: 0.98 to 19.07, p = 0.041).

In the analysis by protocol, the rate of the number of total events / patients with hypoglycemia in the "physiological" group was 2.4 ± 1.3 events / patient, while in the traditional group it was 1.6 ± 0.7 events / patient (p = 0.129) ; in the intention-to-treat analysis in the "physiological" group it was 2.5 ± 1.6 events / patient, whereas in the traditional group it was 1.7 ± 0.9 events / patient (p = 0.182)

Thirty-eight hypoglycemic events were found in the "physiological" group and 26 hypoglycemic events in the traditional group; of which, 36 were mild hypoglycemia in the "physiological" group and 24 events in the traditional group (RR per protocol: 1.02, 95% CI: 0.91 to 1.19, p = 1.0; RR by intention to treat: 1.03, 95% CI: 0.90 to 1.17, p = 1.0).

Regarding the complications associated with diabetes, soft tissue infection was the most frequent, one patient had pneumonia, one acute renal failure, one acute

respiratory failure, and no patient presented bacteremia, diabetic ketoacidosis or hyperosmolar state. Two of the patients included in the study died from complications not associated with hypoglycemia, one in the physiological group secondary to progression of the infectious process, sepsis and septic shock, and one in the group Traditionally associated with acute respiratory failure.

SECONDARY RESULTS

There was a significant difference in the sustained control of blood glucose that was reported in 20 (55.6%) of the cases in the physiological group compared to 30 (76.9%) of the traditional group (per protocol, RR: 0.74, 95% CI: 0.58 to 0.94, p = 0.009; by intention to treat, RR: 0.72, 95% CI: 0.51 to 1.01, p = 0.049).

The causes of failure of the sustained control were discharge before control in goals, progress to critical state, death before glycemic control, poor adherence to the protocol and suspension for sustained hypoglycemia. With the "physiological" scheme it was necessary to suspend or change by another scheme in 8 (22.2%) patients, in comparison with the traditional scheme where only the scheme was suspended or changed in 1 (2.6%) patient (by intention to treat, RR: 8.67, 95% CI: 1.14 to 65.92, p = 0.011). There were no adverse effects to the use of insulin in both groups.

OTHER RESULTS

If the suspension of the scheme is considered for sustained hypoglycemia of 8 patients in the physiological group vs 1 patient in the control group, a risk ratio of 8.67 (95% CI: 1.14 to 65.9) and a number necessary to harm of 5.09 was calculated (95% CI: 2.93 to 19.23) patients with the physiological scheme to produce 1 event of hypoglycemia.

INFORMED CONSENT

INFORMED CONSENT
Date:
Registry number:

Comparative study of Physiological insulin scheme vs Traditional scheme for glycemic control in not critical hospitalized patients with type 2 diabetes mellitus.

Responsible researches: José Antonio de Jesús Álvarez Canales
Thesis: Paulina Berenice Crespo Morfin
Institution: University of Guanajuato Division of Health Sciences
Place where the study will be conducted: General Hospital León.

You are being invited to participate in this medical research study. Before deciding if you accept or not, you must know and understand each of the following sections. This process is known as informed consent. Feel absolutely free to ask about any aspect that helps you to clarify your doubts about it. Once you have understood the study and if you wish to participate, then you will be requested to sign this informed consent, from which will be delivered a signed and dated copy.

Justification of the study:

High and low glucose (blood sugar) in patients admitted to a hospital is a common health problem, which generates high costs to hospitals and is associated with an increased risk of complications and death.
The control of blood sugar levels and the choice of insulin schemes (medicine to control high blood sugar) has been controversial. The "physiological" insulin regimen is recommended by the American Diabetes Association for the non-critical hospitalized patient, however, it has an increased risk of hypoglycemia (low blood sugar).

Objectives of the study:

You are being invited to participate in a research study which has the purpose to:
find if it is better the Physiological Scheme or the Traditional Scheme of insulin for the control of blood sugar in patients with type 2 diabetes.

Benefits of the study:

By means of this study we pretend to find which insulin scheme is more effective and safer for the hospitalized patient with type 2 diabetes mellitus.
This represents fewer symptoms and complications during your hospital stay, less time to control your sugar, and less costs.
In previous studies by other researchers, it has been observed that the "physiological" scheme is the best for lowering high blood sugar, although there are other studies about the low sugar it generates. There are few studies that show if the traditional scheme is as effective as the physiological scheme and with less risk of low blood sugar.

This study will allow future patients to benefit from the knowledge we acquire from this study, by implementing a new treatment proposal or defending the one currently established.

Study procedure:

The next study will consist in selecting two groups to apply insulin in the arm as management and control of type 2 diabetes mellitus during their hospital stay. A group with a physiological insulin scheme consisting of four insulin applications per day, the second group of a traditional scheme consisting of two insulin applications per day. If the blood sugar levels are higher than expected, doses of supplemental

insulin will be applied. If blood sugar levels are lower than expected, the dose of sugar will be applied through the vein. A picket will be taken on the finger every 4 hours to monitor blood sugar levels and based on that result the insulin adjustment will be made. You may present the next symptoms in case of hypoglycemia: sweating, chills, dizziness, nausea, feeling hungry, blurred vision, numbness, paresthesia in lips or tongue. In this case a qualified nurse must be informed for proper treatment and to raise blood sugar levels.

You cannot choose a group to pertain. The selection will be made at random. Upon leaving from your hospitalization you will receive a report of the outline of what was selected with the optimal insulin dose calculated for you.
If you present adverse effects, the specialist will decide if the treatment will be changed or even the possibility of suspending the insulin.

Clarifications:

-You can deny participating in the study. The decision to participate is completely voluntary.
- Your personal data are confidential and will be safeguarded for research purposes and will be protected in accordance with the law of protection of personal data.
-In the course of the study you can request to the responsible researcher for updated information about it.
-There is no risk in participating in this study.
Informed consent letter.
I, _____, have read and understood the above information and my questions have been answered satisfactorily. I have been informed and I understand that the data obtained in the study can be published or disseminated for scientific purposes. I agree that I participate in this research study. I will receive a signed and dated copy of this consent form.

_____
SIGNATURE OF THE PARTICIPANT

_____
WITNESS 1

_____
WITNESS 2

I have explained the nature of the research, about the risks and benefits involved in their participation. I have answered the questions as much as possible and asked if you have any questions. I accept that I have read and I´m aware of the regulations that are involved with humans' research, and my attachment with the study. Once the question and answer session were concluded, this document was signed.

_____
SIGNATURE OF THE MAIN INVESTIGATOR