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# EFFICACY AND SAFETY OF NPH INSULIN IN THREE DOSES COMPARED WITH INSULIN GLARGINE IN HOSPITALIZED PATIENTS WITH DIABETES MELLITUS: A PHASE II CLINICAL TRIAL IN HOSPITAL

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**Abstract: Background:** Insulin management with the basal bolus method is indicated in the diabetic patient admitted to the hospital ward. Few studies exist to suggest the best regimen to manage hyperglycemia in hospitalized patients. **Material and metohds:** It is a controlled, randomized, single-blind clinical trial. Forty-two participants were randomized into two groups, the first with a basal-bolus regimen with insulin glargine once a day and insulin lispro before each meal, the second with insulin three times a day with regular insulin before each meal. **Results:** No statistically significant difference was found in the daily glucose control goal. To assess safety, hypoglycemia events were analyzed by group, which did not show a statistically significant difference in both groups (p= 0.428). **Conclusion:** In safety, NPH insulin was similar in the presence of hypoglycemic events when compared to insulin glargine without presenting a significant difference between both groups, in terms of efficacy, no differences were found in achieving the conclusion that they can be used safely and safely. a lower cost.

**Keywords**: Diabetes Mellitus, Isophone insulin therapeutic use, Hypoglycemia, Mexico, Continuous glucose monitoring, Latin America

## INTRODUCTION

According to the ENSANUT survey, it has been estimated that 9.4% of the Mexican population suffers from diabetes mellitus. It is estimated that approximately 40% of hospitalized patients will be discharged with a diagnosis of type 2 diabetes mellitus (DM2), this added to patients with hyperglycemia figures greater than 126 mg/dL and who have not been diagnosed as such. (13, 15) Patients with hyperglycemia have shown an increase in the use of hospital resources and a worse prognosis due to the increase in acute complications. Hospital stay is longer in patients with hypoglycemia than in normal glycemic patients.

In 2010, a study was reported that examined the economic impact of medical care for patients with DM2 at the Mexican Institute of Social Security (IMSS). The direct costs of such care amounted to $452 million, with a cost of $183 million for patients without complications and $269 million for patients with complications. (4, 13)

In the hospital setting, hyperglycemia and hypoglycemia are associated with adverse outcomes including death. Because of that, the goals of hospitalized patients include prevention. (17)

The practical guidelines for glycemic control of the ADA argue for the use of insulin according to its basal secretion, as well as in the intake of food with boluses as required in escalation according to glycometry, thus maintaining a physiological application of insulin in hospitalized patients. . (22)

Strict glycemic control supported by insulin therapy is obviously a process of time and dedication in the management of hospitalized patients who could have major complications such as hypoglycemia that can present from minimal effects to irreversible sequelae as a consequence of inadequate management. Attempts have been made to propose multiple insulin application protocols in order to avoid hypoglycemia. (16, 21, 22)

Strict control of it has been shown in various studies to reduce short- and long-term mortality, multiple organ dysfunction, and systemic infections, as well as a decrease in ICU stay and in the total cost of hospitalization. (4, 23)

Both hypoglycemia and hyperglycemia have been related to unfavorable outcomes in hospitalized patients, including death, which is why it is about finding different management schemes trying to avoid both

situations. (14, 24)

In a meta-analysis of studies of surgical patients diagnosed with DM2, it was observed that patients who documented glucose levels lower than 180 mg/dL were associated with a lower percentage of mortality and heart attack compared to those who maintained a glucose level of 200 mg/dL. dL, while they did not present any additional benefit to those who were established a stricter control lower than 140 mg/dL. Therefore, it was established that insulin must be started in diabetic patients to maintain a glucose goal of less than 180 mg/dL in hospitalized patients. Insulin treatment must be started in all patients who present a glucose figure greater than or equal to 180 mg/dL and once insulin is started it must maintain a glucose range between 140-180 mg/dL in most patients. (1)

The NICE-SUGAR study reported that, in intensive glucose control schemes, there was an increase in mortality and in the number of severe hypoglycemia (less than 40 mg/dL) compared to patients who had moderate glycemic control. (16)

Basal bolus or basal plus insulin regimens are the most recommended schemes for hospitalized patients in the general ward. The Basal-bolus scheme recommended for patients who have an adequate intake of food by mouth, and likewise for fasting patients, or the basal or basal plus insulin scheme for patients who have low oral intake. An intermediate or long-acting insulin and a prandial correction bolus are applied according to the requirement respectively. (twenty-one)

Hence the need to find the best insulin regimen for our patients with the insulins that are available in the hospital environment of our community in Latin America and in the public hospitals of our country. The compounds generally available are human insulins (Neutral Protamin Hagedorn insulin, known as NPH) and rapid-acting insulin (regular insulin). In previous years, some studies were published that demonstrate the superiority of analog insulin in reaching the in-hospital glucose goal with fewer complications, such as hypoglycemia. (6, 19)

However, the availability of analog insulins in the hospital setting is sometimes limited by cost. Because of this, studies with both insulins have been continued planning different insulin regimens to reach the goal in different types of population.

In a study of a rural population, where access to analogue insulins is difficult, insulin regimens with NPH insulin were considered to assess adherence to the basal bolus regimen compared to the escalating rapid insulin regimen. Their adherence was evaluated four months after hospital discharge, demonstrating that the patients achieved improvement in their glycemic control without major hypoglycemic events and adequately maintained the basal bolus regimen with human insulins. (12)

There are few studies carried out in Latin America that suggest the best regimen for treatment of hospitalized patients with DM2. In general, the guidelines from the United States of America are used even when there are large differences in the characteristics of the Latino population, such as demographics, reason for admission, availability of hospital resources, and glucose level at hospital admission. In 2015, in Asunción, Paraguay, a study of 134 patients was carried out comparing NPH insulin in two doses against insulin glargine. Similar results were obtained in terms of efficacy and safety between both insulins, only showing a greater number of hypoglycemias in the NPH insulin group, none of which was severe. (2)

This increase in the number of hypoglycemias in the NPH group could be attributed to the fact that two doses were administered, which caused an overlapping of

the different insulin action times and its dose. In the two-dose regimen, NPH insulin was administered two-thirds in the morning and one-third in the evening, thus having a much longer action time in the morning and less in the afternoon. Which leads one to think, if the total amount of insulin is administered, but administered in three doses, it could reduce these overlapping actions. Thus avoiding hypoglycemia and maintaining target control for hospitalized patients.

This leads to the understanding that both insulins have similar effects as long as they are administered in such a way that they maintain an action in the body of the same characteristics. If NPH insulin is administered in 3 doses, it would maintain an effect curve similar to that of analogous glargine insulin, with slight peaks of action that could act on the prandial need for insulin, behaving appropriately to maintain the goals established for the patients.

Safety is understood when the patient undergoing treatment with insulin therapy has the target glycemic control established by the ADA guidelines for the management of hyperglycemia, without presenting the main complication of insulin therapy, hypoglycemia.

Hypoglycemia is defined as low glucose less than 70 mg/dL with glycopenic or neuroglycopenic symptoms or glucose less than 50 mg/dL without symptoms. Below these levels, complications in terms of mortality, days of hospital stay, and costs increase considerably with an impact on patient outcome, which is reason enough to avoid this complication at all costs. (22)

There are some triggering or adjuvant events in presenting a hypoglycemic event in patients receiving insulin therapy, such as reduced oral intake, total fasting, inappropriate time between the application of insulin and oral intake, decreased infusion of glucose sera, abrupt interruption of oral or parenteral nutrition. This culminates in neurological deterioration. All these events or the possibility of presenting some of them must be attended to to avoid hypoglycemia. (22, 24)

In one study it was observed that 80% of patients who had severe hypoglycemia had previously already presented mild hypoglycemia. Most of these patients had a basal insulin and their insulin dose was not changed despite having low glucose levels. Because of this, insulin dosing must be done daily, both to prevent hyperglycemia and hypoglycemia. Insulin therapy changes must be made every 24 hours at the patient's bedside. (24)

The vast majority of hypoglycemic events can be prevented by careful monitoring of feed dosage. For this, it is necessary to be aware of the triggering events and try to eliminate them in their entirety. (5, 25)

Continuous glucose monitoring is defined as continuous interstitial fluid glucose measurement that displays minute-by-minute glucose measurements through different devices.

The free style libre® glucose sensor is a continuous glucose monitoring system that measures through a filament the amount of glucose that exists in the interstitial fluid by means of an electrode coated with glucose oxidase. This system allows knowing the patient's glucose status and glucose trends, which makes it a superior technology in detecting and preventing hypoglycemia compared to intermittent capillary blood glucose monitoring. (7, 9)

Some studies have been carried out that show that the use of continuous glucose monitoring does not improve the glucose level or influence the glycemic control of patients, but if it reduces the presence of hypoglycemia and even through trends it helps to prevent

them, when It is compared with the traditional capillary glucometer system. (10, 18)

In hospitalized patients, glucose monitoring must be performed at least 3 times a day preprandially, that is, before each meal, and for patients who are fasting, they must be monitored at least every 4 hours. for correct glucose correction and daily insulin dosage. This implies at least 3-4 fingersticks per day. (1)

Due to this, a need has been established for a higher technology element that can monitor glucose without the need for multiple punctures per day. Concordance studies were carried out for the use of the glucose monitoring sensor compared against the gold standard of daily life, which is the glucometer, as well as against the laboratory gold standard, which is venous glucose, thus reporting an error grid of consensus as an element to evaluate the accuracy of the glucose meter of 99.7% compared to the glucometer, in zone A+B, this corresponds to zone A where the values are clinically accurate and zone B where the values deviate but are not make changes in treatment. When compared against venous blood glucose it had a 96.5% concordance of clinically accurate results. (8)

The use of NPH insulin in three doses has been proposed as an alternative to achieve the glycemic goal, with greater safety by reducing hypoglycemic events. It is essential to establish a regimen for timely detection of hypoglycemia, as well as its management to avoid subsequent complications. In this context, the therapeutic potential of safety and effectiveness of NPH insulin in three doses could be explored.

## MATERIAL AND METHODS

Prior authorization from the ethics and research committees to carry out this study, the patient was informed of the details of the study for his written informed consent. It is declared that the research was carried out in accordance with the agreed principles on research in human beings in the Declaration of Helsinki and its subsequent amendments, as well as in accordance with the Official Mexican STANDARD NOM-012-SSA3-2012, which establishes the criteria for the execution of research projects for health in human beings. It is a randomized, controlled, single-blind clinical trial. Forty-two participants were randomized into two groups, the first with a basal-bolus regimen with insulin glargine once a day and insulin lispro before each meal, the second with insulin three times a day with regular insulin before each meal. Insulins were assigned to patients under the choice of a sealed envelope. Only the treating physician knows the type of insulin to which he has been assigned. Previously used oral hypoglycemic therapies or insulin therapies were discontinued at the time of hospital admission. The initial dose of insulin was calculated at 0.1-0.2 U/kg/day, if glucose was 140-200 mg/dL and 0.3-0.5 U/kg/day, if glucose was 201-400 mg/dL for both. groups. The calculated dose was divided into three doses for the NPH patients and the total dose was applied for the insulin glargine group, starting in the morning before breakfast. The insulin dose was adjusted daily during the morning visit. If it was greater than 180 mg/dL, fasting glucose was increased by 20%. On the other hand, if it was less than 70 mg/dL, it was decreased by 20%. If preprandial glucose levels were greater than 180 mg/dL, a bolus of analogue or human rapid insulin was added, depending on the case, according to the pre-established scheme, as indicated by the guidelines for intrahospital glycemic control, correcting 1 unit of rapid insulin for every 40 mg/dL. dL of glucose above 180 mg/dL considered as the in-hospital glucose goal, starting at 4 units. For glucose monitoring, the puncture-free continuous monitoring glucose

sensor was applied to the forearm as suggested in the free style libre® glucose sensor user manual. The patient was explained how the sensor worked. The sensor was placed at the patient's admission. The nursing staff recorded with the glucose sensor by means of scanning, according to the manufacturer's instructions, the pre and postprandial blood glucose levels (breakfast, lunch and dinner) and at midnight. Every day, a researcher analyzed the blood glucose values of each patient and recorded them on the data collection sheet. The insulin scheme was adjusted according to the previously mentioned guidelines.

In the univariate analysis of the quantitative variables, measures of central tendency (mean and median) and dispersion (standard deviation) were made, and of the qualitative variables, frequencies and percentages. In the bivariate analysis to contrast the hypotheses of the quantitative variables, the Student's t or Mann-Whitney U test was used according to their distribution, for the categorical variables the $\chi 2$ test was performed. In all cases, a value of p= 0.05 and a 95% confidence interval were accepted. The glucose means obtained in the patients over 5 days during the 6 times that must be measured throughout the day were compared. Likewise, hypoglycemic events were compared between the two groups of patients.

## RESULTS

Of the total number of patients admitted to the Internal Medicine service in the period from September 2019 to January 2020, 58 subjects met the inclusion criteria when randomizing them, the groups were made up of 32 to the insulin glargine group and 26 to the NPH insulin group.

16 subjects were eliminated for dying during the days of the study due to causes unrelated to the intervention of the study.

Forty-two patients were included, of whom 23 were assigned to the insulin glargine group and 19 to the NPH insulin group.

Shapiro-Wilk tests were performed to know the distribution of the population, which was normal, but since it does not meet all the assumptions and the population is less than 20, it is decided to carry out the analysis with non-parametric tests for a non-parametric distribution. normal.

All the sociodemographic variables were compared and it was found that they were homogeneous between the characteristics of both groups, taking a value of $p<0.05$. (Table 1).

To evaluate the efficacy, the median glucose on admission was determined, which was 219 mg/dL (181-273) with no significant difference in both groups (p= 0.96). Subsequently, the mean daily glucose was determined in both treatment groups.

During the 5 days observed, no statistically significant difference was found in the mean daily glucose between the two groups studied with the different insulin schemes. (Table 2)

The glucose mean presented a slight elevation at the end of the day in the group of patients with insulin glargine. (Graph 1) that did not show a statistically significant difference between both groups ( Table 4)

Regarding the average glucose, it can be observed that day by day it decreased in a similar way in both patients. (Graph 2)

During the five days observed, no statistically significant difference was observed in relation to the glucose goal reached, nor in the final goal (Table 3).

To assess safety, hypoglycemia events were analyzed by group, which resulted in 6 hypoglycemia events for the NPH group and 9 events for the glargine group (p= 0.428), which was similar for both groups. (Table 5)

## DISCUSSION

There are few studies in Latin America

comparing the different types of insulin in the population with these characteristics. It is important to know that the demographic characteristics of our population can influence the outcome of the response to the application of treatment, unlike what has been reported in the literature. In our study we found that both insulin regimens resulted in adequate glycemic control, keeping the mean glucose below 180 mg/dL in both groups without presenting significant differences between groups. These results contrast with those reported in the literature where in the North American population analogous insulin such as Glargine had resulted in greater glycemic control when compared to NPH human insulin. (3) However, the studies carried out in Latin America coincide with the results obtained reporting adequate control with human insulins, with the exception of a greater presence of hypoglycemia. (2) In our study, no differences were reported between the two groups, remembering that the application of NPH insulin in three doses would imitate the behavior of analog insulin, and would avoid prolonged action peaks that hospitalized patients with fixed meal times could achieve. greater safety and avoid hypoglycemia.

This study makes us highlight that in Latin America and with the diet established for our population and following the region's schedules, NPH human insulin in a three-dose regimen resulted in adequate glycemic control by reaching the mean glucose during hospitalization, being Thus, an appropriate option for its use, regardless of the reason for admission or its demographic variables in a homogeneous group.

In previous studies, the NPH insulin regimen, when compared to the analogue insulin glargine, had resulted in similar glycemic control, achieving the in-hospital goal, obtaining a mean of 180 mg/dL, using a regimen in two divided doses, the total dose calculated by day in a proportion of two thirds in the morning before breakfast and the remaining third at night before dinner, with the difference of presenting a greater number of hypoglycemias in the NPH group. (2-4)

In our study we divided the total dose of insulin into three equal doses in one third before each meal, thus achieving the same dose, but in a homogeneous distribution that makes a safe and continuous basal action. With this regimen, it was demonstrated that the in-hospital glucose goal was reached and the presence of hypoglycemic events without significant difference between the two groups, unlike what was reported in the literature. (23)

In the RABBIT 2 study, an insulin application regimen with analogous insulins such as insulin glargine in basal application is proposed compared with the bolus regimen of regular human insulin. This study shows that the basal insulin regimen compared to the bolus insulin regimen is superior both in glycemic control and in fewer hypoglycemic events. (twenty)

In the DEAN study, they proposed a comparative study between human and analog insulins, evaluating their effectiveness both in reaching the goal and in their safety. However, this study has the weakness of being carried out in a North American population where both the diet and the hospital admission diagnoses are completely different and these results cannot be reproduced in our Mexican or Latin American population in general. (3) Hence the importance of continuing to study the best insulin regimen for our population.

The other point to discuss is the cost of analog insulin compared to NPH insulin, the latter being the lowest cost and the most widely available in the basic insulin chart in public hospitals. It is important to propose an insulin regimen that achieves glycemic control with the fewest number of hypoglycemic events at the lowest cost. (8,11)

## CONCLUSIONS

In this study, it was found that the regimen in three doses was similar both in safety and in glycemic control when compared with analogous insulin glargine, concluding that the alternative hypothesis cannot be accepted as there is no significant difference in both groups.

In terms of safety, NPH insulin was similar in the presence of hypoglycemic events when compared to insulin glargine, with no significant difference between the two groups, leading to the conclusion that they can be used safely and at a lower cost.

NPH insulin in a three-dose regimen has resulted, in this study, with similar results in achieving the established mean glucose level of less than 180mg/dL, as the glucose goal in hospitalized patients, with no significant difference when compared with human insulins.

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## TABLES

| | NPH insulin | | Insulin glargine | | |
|---|---|---|---|---|---|
| Number of patients | 19 | | 23 | | *p** |
| Age | 57 | (50-66) | 62 | (56-69) | 0.35 |
| Weight | 79 | (65-85) | 70 | (60-83) | 0.23 |
| Size | 1.68 | (1.57-1.72) | 1.65 | (1.6-1.7) | 0.63 |
| BMI | 27.68 | (24.8-33.2) | 27.34 | (22.03-31.14) | 0.63 |
| Md time | 17 | (10-20) | 20 | (10-30) | 0.44 |
| Glucose income | 219 | (181-273) | 226 | (187-277) | 0.96 |

The variables are expressed in median and length Inter quartile 25-75

* Mann–Whitney U

IMC: : Body mass index, DM: Diabetes mellitus

Table I. Characteristics of the population

| | NPH | | Glargine | | *p** |
|---|---|---|---|---|---|
| Average, day 1 | 171 | (146-232) | 194 | (161-221) | 0.59 |
| Average, day 2 | 164 | (117-185) | 154 | (138-202) | 0.48 |
| Average, day 3 | 143 | (112-198) | 145 | (120-186) | 0.74 |
| Average, day 4 | 140 | (104-166) | 130 | (114-158) | 0.56 |
| Average, day 5 | 140 | (124-157) | 138 | (106-168) | 0.79 |

The variables are expressed in median and length Inter quartile 25-75

* Mann–Whitney U

Table II. Glycemic control in patients treated with NPH insulin and insulin glargine (mg/dL)

| | Glargine (n=23) | NPH (n=19) | *p.* |
|---|---|---|---|
| **Goal, day 1** | 10 (50%) | 10 (50%) | 0.55* |
| **Goal, day 2** | 16 (57.1%) | 12 (42.9%) | 0.66* |
| **Goal, day 3** | 17 (54.8%) | 14 (45.2%) | 0.98* |
| **Goal, day 4** | 21 (56.8%) | 16 (43.2%) | 0.64** |
| **Goal, day 5** | 20 (52.6%) | 18 (47.4%) | 0.61** |
| **Goal** | 20(55.6%) | 16 (44.4%) | 0.99** |

* Pearson chi-square

**Fisher's exact test

Table III. Patients with goal achieved

| Day | Timetable of meals | NPH (n=23) | Glargine (n=19) | $p^x$ |
|---|---|---|---|---|
| Day 1 | Fast | 174 (142-240) | 167 (142-200) | 0.97 |
| | Post breakfast | 179 (140-230) | 167 (150-250) | 0.98 |
| | Pre meal | 192 (156-270) | 191 (166-232) | 0.84 |
| | Post meal | 204 (170-253) | 190 (147-241) | 0.38 |
| | Pre dinner | 179 (124-260) | 198 (133-230) | 0.82 |
| | post dinner | 185 (113-238) | 187 (137-232) | 0.71 |
| Day 2 | Fast | 122 (100-166) | 133 (88-182) | 0.56 |
| | Post breakfast | 143 (109-197) | 171 (129-197) | 0.20 |
| | Pre meal | 152 (118-215) | 192 (147-261) | 0.13 |
| | Post meal | 172 (126-221) | 190 (130-228) | 0.70 |
| | Pre dinner | 146 (114-225) | 152 (116-235) | 0.78 |
| | post dinner | 157 (114-240) | 167 (113-258) | 0.72 |
| Day 3 | Fast | 125 (86-167) | 122 (99-164) | 0.95 |
| | Post breakfast | 159 (100-193) | 138 (96-195) | 0.80 |
| | Pre meal | 154 (116-208) | 156 (100-199) | 0.71 |
| | Post meal | 152 (131-229) | 190 (140-210) | 0.75 |

| | | | | |
|---|---|---|---|---|
| | Pre dinner | 126 (112-211) | 161 (127-199) | 0.31 |
| | post dinner | 141 (130-180) | 158 (138-201) | 0.46 |
| Day 4 | Fast | 112 (83-129) | 98 (82-148) | 0.92 |
| | Post breakfast | 130 (96-186) | 137 (96-181) | 0.92 |
| | Pre meal | 154 (109-200) | 155 (98-182) | 0.78 |
| | Post meal | 162 (109-220) | 145 (111-185) | 0.65 |
| | Pre dinner | 154 (121-177) | 150 (114-168) | 0.63 |
| | After dinner | 153 (116-170) | 170 (115-190) | 0.25 |
| Day 5 | Fast | 115 (90-143) | 137 (86-150) | 0.43 |
| | Post breakfast | 138 (115-170) | 140 (98-165) | 0.95 |
| | Pre meal | 155 (121-176) | 124 (98-167) | 0.15 |
| | Post meal | 151 (128-188) | 152 (85-193) | 0.50 |
| | Pre dinner | 153 (114-169) | 140 (110-174) | 0.96 |
| | After dinner | 134 (91-168) | 151 (124-180) | 0.10 |

The variables are expressed in median and length Inter quartile 25-75

* WhitneyMann–Whitney U

Table IV: Glucose per day at different meal times (mg/dL)

| | NPH | glargine | *p** |
|---|---|---|---|
| Sí | 6(31.6%) | 9(60.9%) | 0.42 |
| No | 13(68.4%) | 14(39.1%) | |

* Fisher's exact test

Table V. Events of Hypoglycemia

## FIGURES

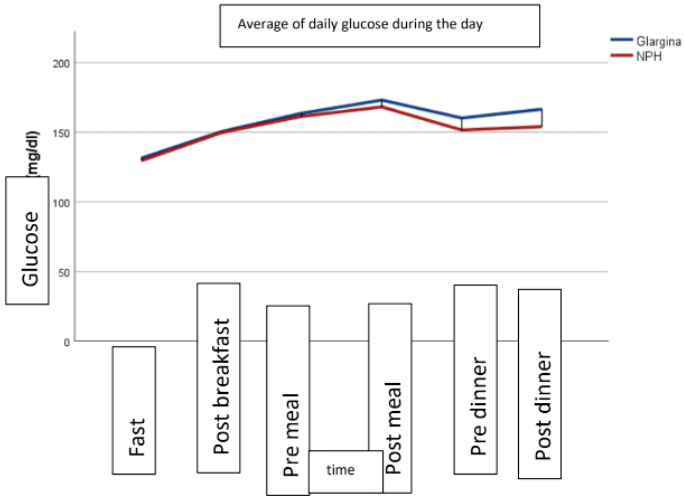


Figure 1. Glucose behavior in both insulin groups throughout the day.

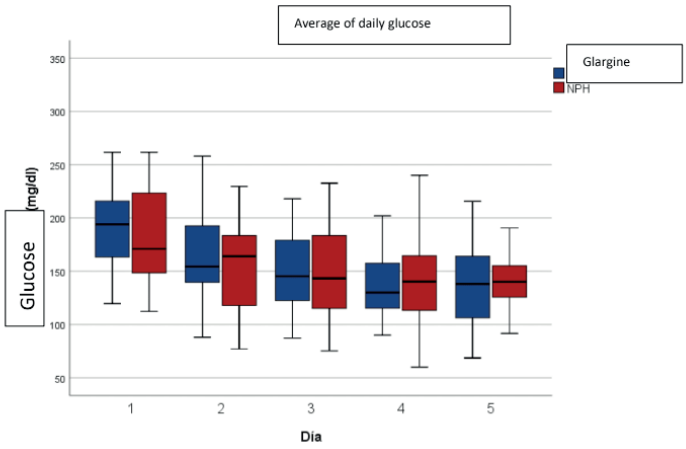


Figure 2. Behavior of glucose in both insulin groups during their hospital stay..