EFFICACY AND SAFETY OF NPH (NEUTRAL PROTAMINE HAGEDORN) INSULIN COMPARED WITH INSULIN GLARGINE IN PATIENTS WITH TYPE 2 DIABETES

PETRA KLANAC[1#], MARKO KAŠTELAN[1#], IVANA KRALJEVIĆ[1,2], TOMISLAV BULUM[1,3], ANELA NOVAK[4], ANNEMARIE BALAŠKO[2], MAJA JURIĆ SAMARDŽIĆ[5], KARIN ZIBAR TOMŠIĆ[2], MAJA BARETIĆ[1,2], MAJA MIKOLAJ KIRIĆ[6], TANJA MILIČEVIĆ MILARDOVIĆ[4], HRVOJE POPOVAC[2], TANJA ŠKORIĆ POLOVINA[2], MARIJA TRIPOLSKI[7], TATJANA BAČUN[7,8], MIRSALA SOLAK[2], SIDBELA ZUKANOVIĆ[5], TINA DUŠEK[1,2], DARKO KAŠTELAN[1,2]

[#]AUTHORS P. KLANAC AND M. KAŠTELAN CONTRIBUTED EQUALLY TO THIS PAPER.

[1]University of Zagreb School of Medicine, Zagreb, Croatia; [2]Department of Endocrinology, University Hospital Center Zagreb, Zagreb, Croatia; [3]University of Zagreb School of Medicine, Department of Diabetes, Endocrinology and Metabolic Diseases, University Hospital Merkur, Zagreb, Croatia; [4]University of Split School of Medicine, Department of Endocrinology, University Hospital Center Split, Split, Croatia; [5]Department of Internal Medicine, General Hospital Slavonski Brod, Slavonski Brod, Croatia; [6]Department of Internal Medicine, County Hospital Čakovec, Čakovec, Croatia; [7]Department of Endocrinology, Clinic for Internal Medicine, University Hospital Center Osijek, Osijek, Croatia; [8]Faculty of Medicine, University Josip Juraj Strossmayer in Osijek, Osijek, Croatia

Abstract

Background: Insulin therapy is often required for achieving adequate glycemic control in patients with type 2 diabetes mellitus (DM2). For that purpose, the insulin analogue glargine is most commonly used in clinical practice, while only a minority of patients are given the cheaper NPH (Neutral Protamine Hagedorn) human insulin. ***Methods:*** In this observational multicenter study we compared the efficacy and safety of insulin glargine and human NPH insulin. During a six-month follow-up period two groups of patients with DM2 were observed. One group was administered NPH insulin while insulin glargine was administered in the other group (53 and 48 participants, respectively). ***Results:*** After six months, both patient groups achieved the same hemoglobin A1c (HbA1c) level (7.5 ± 1 %). In both groups a small statistically nonsignificant increase in body weight was observed. The daily dose of insulin (measured in international units, IU) was significantly higher in the glargine group than in the NPH insulin group (22.4 ± 8.5 IU *vs* 18.6 ± 7.8 IU). The incidence of hypoglycemia was similar in both groups. ***Conclusion:*** Our study revealed no significant difference in the risk of hypoglycemia or in efficacy between insulin glargine and NPH insulin in patients with DM2. Accordingly, our results suggest that human NPH insulin may be an effective and safe treatment for the majority of patients with DM2.

Keywords: type 2 diabetes mellitus, insulin glargine, NPH insulin, hypoglycemia, long-acting insulin

Corresponding author: Prof. Darko Kaštelan, MD, PhD
University of Zagreb School of Medicine,
Department of Endocrinology,
University Hospital Center Zagreb,
Kišpatićeva 12, 10000 Zagreb, Croatia
Tel: +385 98 620 336
darko.kastelan@kbc-zagreb.hr

INTRODUCTION

In the last three decades, the prevalence of diabetes mellitus (DM) has increased fourfold, mainly due to the worldwide increase in obesity. The current prevalence of DM is around 9 %, and DM type 2 (DM2) contributes to 90 % of all DM cases, which makes DM2 an important public health issue (1).

The treatment of DM2 usually begins with a combination of lifestyle changes and peroral antidiabetic medications. Unfortunately, in a large proportion of DM2 patients this combination does not lead to adequate glycemic control (2). In the case of poor glycemic control, insulin treatment is sometimes needed in patients with DM2 (3). Neutral Protamine Hagedorn (NPH) insulin, a synthetic basal human insulin created using a recombinant DNA (deoxyribonucleic acid) technology, has been used in DM2 patients for decades. However, in the last twenty years, a new class of insulin, so-called insulin analogues, has been developed with the main goal to modify and improve insulin pharmacokinetic properties. The chemical structure of insulin analogues differs from the structure of NPH insulin in several amino acids, which partially changes their pharmacokinetic profile. As a result, insulin analogues do not show peak activity (typically occurring 4 – 6 hours after NPH administration), which ensures uniform insulin activity during its action (4). Accordingly, phase III clinical trials demonstrated that administration of the insulin analogue glargine was associated with a lower incidence of hypoglycemia episodes compared to NPH insulin (5).

However, further studies that reflected everyday clinical practice reported contradictory results regarding the frequency of hypoglycemia in patients treated with insulin analogues or NPH insulin (6, 7). For example, a recent meta-analysis showed no difference between insulin glargine and NPH insulin in the occurrence of severe hypoglycemia (6). Lipska et al. also reported that the choice of basal insulin in DM2 patients did not affect the frequency of hospital admissions due to hypoglycemia (7).

The controversial results of previous studies, the fact that patients with DM2 are generally less prone to hypoglycemia due to insulin resistance, as well as the cost of treatment, which is considerably higher for insulin analogues compared to NPH insulin, question the validity of insulin analogue usage in a situation where a potentially equally efficacious and safe, and yet cheaper, alternative is available (8-10). Since data on this topic are still rather scarce, the main aim of the study was to compare the risk of hypoglycemia and efficacy when using NPH insulin and insulin glargine in patients with DM2 in everyday clinical practice.

METHODS

Patients

This observational multicenter study was conducted between June 2019 and June 2021 across five hospitals in Croatia (University Hospital Zagreb, University Hospital Osijek, University Hospital Split, Clinical Hospital Merkur, and County Hospital Slavonski Brod). Patients aged 18 - 85 years with a confirmed diagnosis of DM2 and inadequate blood glucose control during the use of oral antidiabetic drugs (OAD) for at least three months (HbA1c > 7 %) were enrolled. The study did not include patients with a confirmed diagnosis of DM type 1, body mass index < 20 kg/m^2 or > 35 kg/m^2, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 body surface area, treatment with corticosteroids or glucagon-like peptide-1 agonists, pregnancy, liver cirrhosis, heart failure, and active alcohol or drug abuse. Informed consent was obtained from all patients before initiating procedures related to the study, in accordance with the principles of the Helsinki Declaration. The study was approved by the University Hospital Zagreb and the University of Zagreb School of Medicine ethics committees.

Study protocol

The study protocol consisted of a baseline visit and three follow-up visits. At the baseline visit, data about medical history, duration of DM2, previous diabetes treatment, and family medical history were obtained. In addition, all patients underwent weight and height measurements, as well as routine laboratory investigations. Insulin treatment with either NPH insulin or insulin glargine was initiated, depending on the physician's preference. Insulin was administered once daily, between 9 pm and 11 pm, and the starting dose was either 10 international units, IU, or 0.2 IU/kg of body weight, also depending on the physician's preference. The patients were educated about insulin self-administration and self-monitoring of blood glucose levels by a certified nurse educator. They were advised to increase the insulin dose by 2 IU every three days until fasting glucose reached the level of < 7 mmol/L. On the other hand, in the case of a hypo-

glycemic event (glycemia < 3.9 mmol/L) the patients were advised to decrease the insulin dose by 2 IU. Along with the insulin treatment, they continued to take their oral hypoglycemic medications with the exception of sulfonylureas, where dose reduction or discontinuation was considered. The patients were instructed to measure fasting glucose levels every morning, using a standardized glucometer, and to record any hypoglycemic events. At the first follow-up visit, performed 2 – 4 weeks after the baseline visit, insulin doses were revised based on the fasting glucose levels and episodes of hypoglycemia recorded by the patients. The second and the third (final) follow-up visits were performed three and six months after the initiation of insulin treatment, respectively, during which body weight, insulin doses, frequency and severity of hypoglycemic episodes, and HbA1c levels were assessed.

The primary endpoints of the study were a change in HbA1c levels and the incidence of hypoglycemic episodes, whereas the secondary endpoints included changes in body weight and proportions of patients with adequate glycemic control at the end of the study.

Hypoglycemic episodes were categorized as mild, moderate and severe. Mild hypoglycemia was defined as a plasma glucose level between 3 and 3.9 mmol/L, whereas moderate hypoglycemia was defined as a plasma glucose level < 3 mmol/L, both of which could be associated with the presence or absence of mild to moderate hypoglycemic symptoms. In contrast, severe hypoglycemia was defined as an episode of hypoglycemia associated with symptoms during which the patient required the assistance of another person.

Statistical analysis

Statistical analysis was done using SPSS 17.0 (SPSS, Chicago, USA), with significance set at $P < 0.05$. Variables were described as mean and standard deviation. A difference between two independent numerical variables was tested using Student's t-test, and the Chi-square test was applied to test a difference between two categorical variables. The analysis of repeated samples was done using the Wilcoxon test.

RESULTS

A total of 101 patients, 53 treated with NPH insulin (NPH group) and 48 treated with glargine (glargine group), were included in the study. At enrollment, the study subjects were taking 1–4 OADs (metformin and/or dipeptidyl peptidase, DPP4, agonist and/or sulfonylurea and/or pioglitazone). Twelve subjects were taking one OAD, 45 patients two, 40 patients three, and four study subjects were taking four OADs. Eighty subjects were taking metformin. In the glargine group, 37 patients received glargine-U100, and 11 received glargine-U300.

At baseline, the groups were matched for age, sex, body weight, body mass index (BMI), duration of DM2, use of metformin, number of OADs before insulin administration, and initial insulin dose. The baseline HbA1c level was significantly higher in the NPH group compared to the glargine group (9.8 ± 1.6 % *vs* 9 ± 1.3 %, $P = 0.02$). Patient demographics and clinical characteristics are shown in Table 1.

Table 1. *Demographic and clinical characteristics of the patients (N = 101)*

	NPH insulin (n = 53)	**Insulin glargine (n = 48)**	***P***
Sex (male/female) (n)	31/22	29/19	0.84
Age (years)	63.7 ± 9	62.6 ± 9.1	0.63
DM2 duration (years)	11.9 ± 8	12.1 ± 7.6	0.7
Body weight (kg)	83.4 ± 16	84.8 ± 14.4	0.86
Body mass index (kg/m^2)	28.7 ± 4.6	28 ± 3.7	0.82
Number of oral antidiabetic drugs	2.34 ± 0.75	2.38 ± 0.73	0.05
Metformin (yes/no) (n)	42/11	38/10	0.33
Hemoglobin A1c (%)	9.8 ± 1.6	9 ± 1.3	0.02
Initial insulin dose (international units)	15.1 ± 5.9	15.6 ± 5.3	0.53

NPH - Neutral Protamine Hagedorn; DM2 - diabetes mellitus type 2

During the six months of follow-up, no significant difference in the occurrence of hypoglycemic episodes was observed between the treatment groups. Thirteen patients (24.5 %) in the NPH group experienced hypoglycemia, of which 12 patients had blood glucose levels in the range 3 – 3.9 mmol/L, one had blood glucose level < 3 mmol/L, and no patient had severe hypoglycemia. On the other hand, in the glargine group, six patients had a hypoglycemic episode (12.5 %): four of them reported blood glucose levels of 3 – 3.9 mmol/L, one had glucose level < 3 mmol/L, and another one experienced severe hypoglycemia (Table 2). Patients who experienced hypoglycemic episodes had lower end-of-study HbA1c compared to those without hypoglycemia (7 ± 1 % *vs* 7.6 ± 1 %: $P = 0.03$). In both study groups, most hypoglycemic episodes occurred more than 3 months after the start of insulin treatment (NPH group 9/13; glargine group 5/6).

With regard to the efficacy of insulin treatment, no difference was observed between the groups in terms of the target HbA1c values at the end of the study. The level of HbA1c < 7 % was achieved in 17 patients (32.1 %) and 16 (33.3 %) patients in the NPH and glargine groups, respectively. On the other hand, 25 patients (47.1 %) in the NPH group and 21 patients (43.8 %) in the glargine group had HbA1c levels > 7.5 % at the last study visit (Table 3). However, a significantly higher decrease in HbA1c was observed in the NPH group compared to the glargine group (-2.3 ± 1.9 % *vs* -1.5 ± 1.5 %; $P = 0.03$) (Table 2).

At the start of the study, the insulin dose between the groups was not different. In contrast, at the last study visit insulin doses in the glargine group were significantly higher in comparison to the NPH group (22.4 ± 8.5 IU *vs* 18.6 ± 7.8 IU; $P < 0.02$). In both study groups, a modest weight gain was observed during insulin treatment (Table 2).

Table 2. *Clinical characteristics of patients after six months of follow-up (N = 101)*

	NPH group (n = 53)	**Glargine group (n = 48)**	***P***
Hemoglobin A1c (%)	7.5 ± 1	7.5 ± 1	0.95
Δ Hemoglobin A1c (%)	-2.3 ± 1.9	-1.5 ± 1.5	0.03
Body weight (kg)	84.4 ± 14.6	85.4 ± 13.2	0.53
Δ Body weight (kg)	0.63 ± 4.5	0.19 ± 3.7	0.6
Body mass index (kg/m^2)	28.7 ± 4.6	28 ± 3.7	0.82
Insulin dose (IU)	18.6 ± 7.8	22.4 ± 8.5	0.02
Hypoglycemia (n)	13	6	0.06
Mild	12	4	0.13
Moderate	1	1	> 0.999
Severe	0	1	0.47

NPH - Neutral Protamine Hagedorn; IU – international unit

Table 3. *HbA1c after six months of insulin treatment (N = 101)*

HbA1c %	**NPH insulin (n = 53) n (%)**	**Insulin glargine (n = 48) n (%)**	***P***
< 7	17 (32.1)	16 (33.3)	0.84
7 – 7.5	11 (20.8)	11 (22.9)	0.94
> 7.5	25 (47.1)	21 (43.8)	0.92

DISCUSSION

Insulin is one of the most frequently used medications in the treatment of DM2 diabetes, administered to 23 – 26 % of these patients (11, 12). Human insulins were the gold standard in the treatment until the early 2000s when the use of recombinant DNA technology enabled the synthesis of insulin analogues which were expected to have a favorable pharmacokinetic profile. As a result, despite their higher price, insulin analogues have become more popular in everyday clinical practice and their use exceeds that of human insulins (11, 13).

Although randomized clinical trials and meta-analyses reported some benefits of basal insulin analogues compared to human insulins with respect to reduced risk of nocturnal hypoglycemia, insulin analogues have not been shown to reduce the risk of severe hypoglycemia (6, 14–16). In addition, no difference in hospital admissions or emergency department visits related to hypoglycemia was observed between patients on NPH insulin and those on insulin glargine (7). Finally, when compared to NPH insulins, the use of basal insulin analogues was not associated either with better glycemic control or with better clinical outcomes in patients with DM2 (5, 7).

Similar to those reports, our study demonstrated no significant difference in the risk of hypoglycemic events between basal insulin analogues and human insulin, and no difference between the patient groups was observed either in terms of the HbA1c level at the end of the study, which is also in accordance with previous reports (5, 6, 17, 18). However, patients using NPH insulin had a significantly higher decrease in HbA1c levels during six months of treatment compared to those who were taking the basal insulin analogue glargine. This difference can probably be attributed to a higher baseline HbA1c level in the NPH group, as numerous studies have shown that the pretreatment HbA1c level is a key parameter that determines the magnitude of HbA1c decrease during treatment (19–21).

Apart from hypoglycemia, weight gain is another well-known side effect of insulin therapy. Previous studies reported a gain of 3 – 7.5 kg after one year of insulin treatment (22, 23). In our study, body weight remained stable during the six-month treatment period in both study groups, probably owing to the concomitant administration of metformin in a significant proportion of patients. This is in accordance with previous reports showing a positive effect of the insulin-metformin combination on weight gain (23).

Furthermore, the cost of insulin is an important parameter that should be taken into consideration when discussing the treatment of patients with diabetes. A recent paper by Gotham et al. reported that prices of insulin analogues are much higher than NPH insulin prices worldwide (10). Similarly, in the Croatian market insulin glargine is more expensive than NPH insulin by 44 – 105 %, depending on the brand name. Moreover, the results of our study showed that a significantly higher dose of insulin glargine compared to NPH insulin is needed to achieve comparable glycemic control, which further increases the cost of treatment with insulin glargine. These higher costs would be justified in the case of improved glycemic regulation or a decreased risk of adverse effects such as clinically important hypoglycemia and weight gain. However, the present study demonstrated no significant difference in the efficacy and safety profile between insulin glargine and NPH insulin, which is in accordance with previous reports (6, 7). Therefore, the use of insulin analogues might not be justified in the vast majority of DM2 patients.

The strength of our study is reduced by the relatively small number of patients involved, which limits the merits of its results. Accordingly, it is possible that studies with a larger number of participants would obtain somewhat different results. Furthermore, the fact that almost half of the patients in our cohort did not have adequate glycemic control at the end of the study (HbA1c > 7.5 %) could have affected the frequency of hypoglycemia. Likewise, we observed lower end-of-study HbA1c in patients who had hypoglycemia compared to those who did not. Finally, the non-randomized design of the study represents another important limitation as the decision on the type of insulin given to patients, NPH or insulin glargine, was at the discretion of their physicians. Nevertheless, strict and controlled conditions in which randomized clinical trials are conducted differ greatly from everyday practice and, therefore, real-life studies may provide a better insight into the effectiveness of the intervention.

CONCLUSION

Our study revealed no significant difference in the risk of hypoglycemia and efficacy between NPH insulin and insulin glargine in patients with DM2. Accordingly, our

results suggest that human insulin is an effective and safe treatment in patients with DM2.

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SAŽETAK

TERAPIJA BAZALNIM INZULINOM U BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 2; USPOREDBA UČINKA I NUSPOJAVA INZULINSKOG ANALOGA GLARGINA I HUMANOG (NPH, NEUTRAL PROTAMINE HAGEDORN) INZULINA

P. KLANAC[1#], M. KAŠTELAN[1#], I. KRALJEVIĆ[1,2], T. BULUM[1,3], A. NOVAK[4], A. BALAŠKO[2], M. JURIĆ SAMARDŽIĆ[5], K. ZIBAR TOMŠIĆ[2], M. BARETIĆ[1,2], M. MIKOLAJ KIRIĆ[6], T. MILIČEVIĆ MILARDOVIĆ[4], H. POPOVAC[2], T. ŠKORIĆ POLOVINA[2], M. TRIPOLSKI[7], T. BAČUN[7,8], M. SOLAK[2], S. ZUKANOVIĆ[5], T. DUŠEK[1,2], D. KAŠTELAN[1,2]

[#] AUTORI P. KLANAC I M. KAŠTELAN SU JEDNAKO PRIDONIJELI ČLANKU

[1]Medicinski fakultet Zagreb, Sveučilište u Zagrebu, Zagreb, Hrvatska; [2]Zavod za endokrinologiju, Klinički bolnički centar Zagreb, Zagreb, Hrvatska; [3]Zavod za dijabetes, endokrinologiju i metaboličke bolesti, Klinička bolnica Merkur, Zagreb, Hrvatska; [4]Medicinski Fakultet Split, Sveučilište u Splitu, Zavod za endokrinologiju, Klinički bolnički centar Split, Split, Hrvatska; [5]Odjel za internu medicinu, Opća bolnica Slavonski Brod, Slavonski Brod, Hrvatska; [6]Odjel za internu medicinu, Županijska bolnica Čakovec, Čakovec, Hrvatska; [7]Zavod za endokrinologiju, Klinika za unutarnje bolesti, Klinički bolnički centar Osijek, Osijek, Hrvatska; [8]Medicinski fakultet Osijek, Sveučilište Josipa Jurja Strossmayera u Osijeku, Osijek, Hrvatska

Uvod: Terapija inzulinom često je potrebna za postizanje odgovarajućeg nadzora glikemije u bolesnika sa šećernom bolešću tipa 2 (ŠBT2). U tu se svrhu trenutačno u kliničkoj praksi najčešće koristi inzulinski analog glargin, a znatno rjeđe jeftiniji humani inzulin NPH (Neutral Protamine Hagedorn). ***Metode:*** U ovom opservacijskom multicentričnom istraživanju usporedili smo učinkovitost i sigurnost inzulina glargina i humanog NPH inzulina. Tijekom šestomjesečnog razdoblja praćenja promatrane su dvije skupine bolesnika sa ŠBT2. U jednoj skupini primijenjen je inzulin NPH (n = 53), dok je drugoj skupini primijenjen inzulin glargin (n = 48). ***Rezultati:*** Nakon šest mjeseci obje skupine bolesnika postigle su istu razinu hemoglobina A1c (HbA1c) (7,5 ± 1 %). U obje skupine uočeno je blago statistički neznačajno povećanje tjelesne mase. Dnevna doza inzulina (iskazana u međunarodnim jedinicama, IU, od engl. *international units*) bila je značajno veća u skupini koja je primala glargin nego u skupini koja je primala inzulin NPH (22,4 ± 8,5 IU prema 18,6 ± 7,8 IU). Učestalost epizoda hipoglikemije bila je podjednaka u objema skupinama. ***Zaključak:*** Naše istraživanje nije pokazalo značajnu razliku ni u riziku od hipoglikemije niti u učinkovitosti između inzulina glargina i inzulina NPH u bolesnika s ŠBT2. Sukladno tome, naši rezultati upućuju na to da humani inzulin NPH može biti učinkovit i siguran izbor liječenja za većinu bolesnika sa ŠBT2.

Ključne riječi : šećerna bolest tip 2, inzulin glargin, inzulin NPH, hipoglikemija, dugodjelujući inzulin

Autor za korespondenciju: prof. dr. sc. Darko Kaštelan, dr. med.
Medicinski fakultet Zagreb
Sveučilište u Zagrebu
Zavod za endokrinologiju
Klinički bolnički centar Zagreb
Kišpatićeva 12, 10000 Zagreb, Hrvatska
Tel: +385 98 620 336
darko.kastelan@kbc-zagreb.hr