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Neutral Protamine Hagedorn versus Glargine 100 International Units among Elderly Patients with Type 2 Diabetes Fasting Ramadan

Hossam Arafa Ghazi
Department of Internal Medicine, Mansoura Faculty of Medicine, Mansoura, Egypt
***Corresponding author:** Hossam Arafa Ghazi, **Mobile:** (+20) 01006408074, **Email:** hossamghazi7@gmail.com

ABSTRACT

Background: One of the main five pillars of Islam is Ramadan fasting. In Egypt, Muslims usually fast from 12 to 16 hours. Neutral Protamine Hagedorn (NPH) is cheaper basal insulin in comparison to Glargine U100, and has shorter duration of action. Main fear from insulin usage in elderly with type 2 diabetes mellitus (T2DM) in Ramadan is hypoglycaemia. **Objective:** The aim of the present study was to compare the safety and efficacy NPH versus Glargine U100 among elderly patients fasting Ramadan.

Patients and methods: The study was conducted on 100 patients of both genders with T2DM aged 60 years and more. Comprehensive geriatric assessment was done. Weight, glycated haemoglobin (HbA1c) and creatinine (1 month before Ramadan and 2 months after Ramadan) were estimated. Moreover, numbers of documented hypoglycaemia and days of breaking fast were compared.

Results: The mean age of the patients was 65.9 (SD 3.6) years among glargine group, and 66.2 (SD 3.7) years among NPH group, and 58 of the participants were females. There was significant difference in days to break fasting from hypoglycemia [3 days in NPH group versus 10 days in glargine group (P-value 0.03)]. No statistical difference regarding weight and creatinine before and after Ramadan among both groups.

Conclusion: NPH could be a better option than Glargine U100 for elderly patients with T2DM willing to fast Ramadan, with less reported attacks of hypoglycaemia and lower cost.

Keywords: Elderly, Type 2 Diabetes Mellitus, Ramadan Fasting, NPH, Glargine U100.

INTRODUCTION

One of the five main pillars of Islam is Ramadan fasting. Usually, Muslims fast 29 to 30 days from the sunrise (sohor) to sunset (iftar). In Egypt -in the last few years- these fasting hours range from 12 to 16 hours. Although many elderly patients with diabetes have the chance not to fast, but the majority of them refuse this and insist to fast [1]. Moreover, Ramadan fasting may carry some hazards on some patients with diabetes especially elderly patients. First, fluctuation of blood glucose level may occur during fasting (hyperglycaemia and/or hypoglycaemia), increase risk of thromboembolic manifestation and increase risk of ketosis [2].

It's well established that cultural habits of Ramadan fasting have great variability of traditions in different countries and communities. In addition, Muslims in Egypt have the main meal after sunset while another meal is consumed in the midnight. Moreover, Egyptian food during Ramadan usually contains relatively high amounts of carbohydrates and fats [3].

On the other hand, Egypt is listed as one of the top ten countries having large number of people living with diabetes mellitus (DM). According to the International Diabetes Federation (IDF), 10.9 million people living in Egypt having diabetes (in the age range from 20-79 years) in 2021 and it is supposed to be doubled in 2045, reaching about 20 million patients with diabetes [4]. Also, in the last few years it was noticed that there is increase in the relative and absolute number of elderlies in Egypt. Central agency for public mobilization and statistics reported that elderlies represent about 7% of total Egyptian population in 2019, and expected to represent about 12% to the total population by the year 2030 [5]. Prevalence of DM is increased with age, subsequently total number of elderly patients having type 2 diabetes mellitus (T2DM), and fasting Ramadan will increase. Complications of fasting are relatively higher among elderly in comparison to those younger patients [2].

Insulin therapy is the corner stone in treatment of type 1 diabetes, while it is used for treatment of many patients having T2DM. One of the protocols used in our daily practice in management of patients with T2DM is basal oral protocol, in which the basal insulin is introduced (initiated) on top of oral therapy to intensity the control of blood sugar and mainly to reduce the fasting blood sugar rather than the postprandial blood glucose [6].

For physicians treating people with diabetes, the main fear from treating diabetes among general population and particularly elderly patients hypoglycaemia. Moreover, hypoglycaemia is the most famous side effect of insulin therapy and considered as a big barrier for physicians who treat patients with diabetes. This risk is increased in patients who are on insulin therapy. All patients who are willing to fast should be educated to break their fasting when the random blood glucose at any time of fasting become less than 70 mg/dl [3].

Neutral Protamine Hagedorn (NPH) is one of the old human insulins which may be used with short acting regular insulin or with oral anti-diabetic drugs. Once injected subcutaneously its onset of action about 2 hours and its peak appears after 6-14 hours and its duration of action lasts for 10-16 hours. On the other

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hand, Glargine U100 is considered as the first true basal insulin. After subcutaneous injection its onset of action about 2 hours and its duration of action lasts for 20-24 hours [7]. In Egypt, the cost of prefilled cartridge of NPH that contain 300 units is 32 Egyptian pounds, while it is 129 Egyptian pounds for Glargine U100.

However, due to difference in the pharmacokinetics and pharmacodynamics not all insulins are the same regarding risk of hypoglycaemia. From the previous points we started to think why not to use NPH as a basal insulin in Ramadan instead of Glargine U 100 which is a common basal insulin used in the clinical practice among Egyptian patients with T2DM, as it is cheaper and will not continue the whole day, and it is expected that at the end of fasting hours (before iftar) to be at the nadir level in the blood, subsequently the hypoglycaemia events expected to be less in comparison to Glargine which is more expensive, and have longer duration of action.

PATIENTS AND METHODS

A randomized controlled clinical trial was carried out on 100 Egyptian elderly patients attending Geriatric and Diabetes Outpatient Clinics of Specialized Medical Hospital, Mansoura University, and private clinics in the period on Ramadan 2022 (1443 year of Hijra). We included both males and females aged 60 years or older after agreeing to participate in the study. The random blood glucose of participants was <300 mg/dl and Glycated Haemoglobin (HbA1c) <9 gm %.

Exclusions criteria were patients with recently discovered T2DM 3 months before Ramadan, other types of DM rather than T2DM, patients with severely uncontrolled diabetes (HbA1c >9gm % and/or random blood glucose >300mg/dl). Moreover, patients who shouldn't fast according to Diabetes and Ramadan (DAR) recommendations [3] were excluded [like decompensated liver cirrhosis, estimated Glomerular Filtration Rate (eGFR) less than 30 ml/min and hospitalization due to hyperglycemic crisis like diabetic ketoacidosis or hyperglycemic hyperosmolar crisis in last year]. Detailed medical history was taken including drug history and comorbid conditions. General Examination was done for all participants including measurement of brachial blood pressure and body mass index (BMI) before one month before Ramadan fasting and 2 months after Ramadan. HbA1c and creatinine were measured before Ramadan fasting and 2 months after Ramadan, eGFR was calculated using the original Modification of Diet in Renal Disease (MDRD) 4 variable equation.

Patients were divided into 2 groups: ***Group 1*** formed of 50 patients taking Glargine U100 as basal insulin plus their oral drugs, and standard of care. Dose of Glargine U100 was initiated as 10 IU and titrated gradually till making the fasting blood sugar from 80-130 mg. Patients were informed to reduce the basal insulin dose 20% in Ramadan and insulin should be injected at Iftar time. On the other hand, ***Group 2*** was formed of 50 patients were taking NPH as a basal insulin plus their oral drugs and standard of care. Dose of NPH was initiated as 10 IU and titrated gradually till making the fasting blood sugar from 80-130 mg. Patients were informed to reduce the basal insulin dose 20% in Ramadan and insulin should be injected at Iftar time.

The following points were assessed: firstly, 5 Self-Monitoring Blood Glucose (SMBG) readings (2 hours after sohor, 12 pm, 3pm, 1 hour before iftar, 2 hours after iftar) in the first week of Ramadan fasting and/or when sense of any symptoms of hypoglycemia or hyperglycemia at any time of the month. Secondly, number of episodes suggesting hypoglycemia (symptoms of dizziness, visual blurring, palpitations, nausea, sweating, confusion, tremor, or intense hunger with or without biochemical confirmation). Thirdly, number of days the patient break fasting (patients were educated to break fasting immediately if blood glucose less than 70mg/dl or more than 300 mg /dl at any time of fasting). Lastly, changes of weight, eGFR & HbA1c before and 2 months after Ramadan were evaluated. Patients were telephoned every 10 days during Ramadan to assure safety of fasting.

Ethical consent:

Mansoura University's Institutional Review Board approved the study if all participants signed informed consent forms and submitted them to Mansoura University by the code (R.22.04.1675). We adhered to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

Statistical analysis

Data were fed to the computer and analysed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) and mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Chi-Square-test was used for comparison of 2 or more groups for categorical variables. Student t-test was used to compare 2 independent groups. Paired t test was applied to compare between before and after treatment results. The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables. P value ≤ 0.05 was considered significant.

RESULTS

Table 1 Shows that there is no statistically significant difference between the 2 groups regarding sociodemographic characteristics.

Table (1): Comparison of sociodemographic characteristics of the studied groups

Variable	Group 1 (Glargine U100) n=50	Group 2 (NPH) n=50	Test of significance
Age (years) (mean ± SD)	65.94 ± 3.62	66.20 ± 3.74	t=0.380 p=0.704
Sex - Males - Females	 22 (44 %) 28 (56 %)	 20 (40 %) 30 (60 %)	 χ^2=0.164 p=0.685
Special habits - Non-smoker - Ex-smoker -Current smoker	 35 (70 %) 7(14 %) 8(16 %)	 38 (76 %) 6 (12 %) 6 (12 %)	 χ^2=0.486 p=0.784

t: Student t test, χ^2=Chi-Square test

Table 2 shows that there is no statistically significant difference between the 2 groups regarding prevalence of hypertension, duration of diabetes, types of oral antidiabetic drugs and mean dose of basal insulin.

Table (2): Comparison between studied groups regarding hypertension and diabetes & its treatment

Variable	Group 1 (Glargine U100) n=50	Group 2 (NPH) n=50	Test of significance
Frequency of Hypertension	34 (68 %)	38 (76 %)	χ^2=0.794 p=0.784
DM duration (years) median (range) (IQR)	11 (5-21) (8-13.25)	11 (5-21) (8-14)	U=0.069 P=0.945
Metformin	50 (100 %)	48 (96.0 %)	FET=2.04 P=0.153
Vildagliptin	20 (40 %)	13 (26 %)	χ^2=2.22 P=0.137
Gliclazide MR	26 (52 %)	27 (54 %)	χ^2=0.04 P=1.0
Mean dose of basal insulin (IU)	28.76±5.46	30.32±4.98	t=1.49 p=0.139

U: Mann Whitney U test, χ^2: Chi-Square test t: Student t test, FET: Fischer exact test , IQR: Interquartile range

Table 3 shows that HbA1c significantly improved 2 months after Ramadan fasting among 2 groups. In addition, this improvement of glycaemic control is noted to be more significant among glargine U100 group.

Table (3): Comparison between HbA1c one month before & 2 months after Ramadan fasting among studied groups.

Variable		Group 1 (Glargine U100) n=50	Group 2 NPH n=50	Test of significance
HbA1C gm%	Before Ramadan	7.94± 0.51	8.18± 0.52	t=2.26 **p=0.026***
	2 Months after Ramadan	7.57± 0.56	7.79± 0.52	t=2.09 **p=0.039***
		P<0.001*		**P<0.001***

t: Student t test , *statistically significant

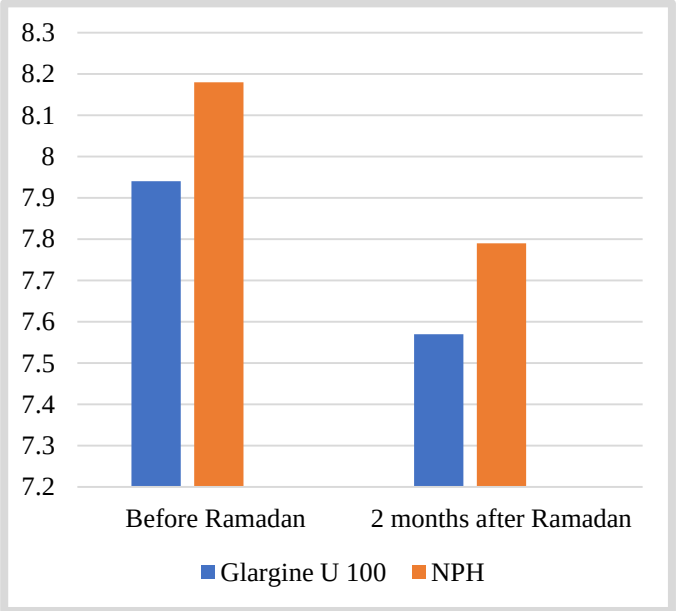

Figure (1): HbA1c difference among 2 groups (one month before Ramadan and 2 months after Ramadan fasting)

Table 4 shows that there is no statistically significant difference between 2 groups regarding BMI before and 2 months after Ramadan Fasting

Table (4): Comparison of BMI one month before and 2 months after Ramadan fasting between studied groups.

Variable		Group 1 (Glargine U100) n=50	Group 2 (NPH) n=50	Test of significance
BMI (kg/m^2)	Before Ramadan	32.53 ± 3.32	32.58 ± 3.32	t=0.078 p=0.938
	2 months after Ramadan	32.48 ± 3.36	32.56 ± 3.35	t=0.116 p=0.908
		P=0.590		**P=0.590**

t: Student t test

Tables 5 shows that there is no statistically significant difference between 2 groups regarding eGFR before and 2 months after Ramadan Fasting

Table (5): Difference in eGFR one month before and 2 months after Ramadan fasting among studied groups

Variable		Group 1 (Glargine U100) n=50	Group 2 (NPH) n=50	Test of significance
eGFR (ml/min /m2)	Before Ramadan	79.88 ± 9.21	80.06 ± 9.92	t=0.094 p=0.925
	2 months after Ramadan	78.58 ± 9.73	79.64 ± 10.26	t=0.530 p=0.597
p=0.136 1.6%			p=0.136 0.52%	

t: Student t test *statistically significant

Table 6 shows that there is no statistically significant differences between 2 groups regarding total numbers of hypoglycemia episodes and days to break fasting from hyperglycemia. However, NPH group has statistically significant lower days to break fasting due to hypoglycemia

Table (6): Comparison between hypoglycemic episodes & number of days to break fasting among studied groups

Variable	Group 1 (Glargine U100) n=50	Group 2 (NPH) n=50	Test of significance
Number of hypoglycemic episodes during Ramadan	8	3	χ^2=2.55 p=0.110
Days to break fasting due to hypoglycemia	10	3	χ^2=4.33 **p=0.037***
Days to break fasting due to hyperglycemia	3	3	χ^2=0.0 p=1.0

χ^2: Chi-Square test *statistically significant

DISCUSSION

In the past, elderly patients with T2DM who are willing to fast are considered high risk categories for fasting. Moreover, a lot of elderlies have the chance not to fast, but majority of them are enjoying Ramadan fasting [8]. Although age itself is considered as a risk factor for Ramadan fasting, but nowadays risk stratification of elderly people with T2DM is not based on age only rather than associated comorbidities & socioeconomic status [3].

In our study, 100 elderly patients were included with mean age about 65.94 years and 66.2 years among Glargine group and NPH group, respectively. Many of our cases were females as 'feminization' is a characteristic features in elderly Egyptian community with 83 men for 100 women sex ratio [9]. Regarding blood pressure, 68 % of Glargine group and 76 % of NPH group were hypertensive. This matchs with results of CAPTURE trial [10] which found that about 70 % of the participants were known to have hypertension. The same also were reported by **Hassanein *et al.*** [11] in a global survey conducted in 2020 during the pandemic of COVID-19 and found that patients with T2DM aged 65 years or more have prevalence of hypertension about 66.69% in comparison to those younger than 65 years with hypertension prevalence about 45.29%.

The mean duration of diabetes among patients was about 11 years. On the other hand, the mean HbA1c before Ramadan fasting was 7.94 gm% and 8.18 gm% among glargine group and NPH group, respectively. After initiation of the basal insulin, the HbA1c is significantly improved among both groups and became 7.57 gm% and 7.79 gm% among Glargine group and NPH group, respectively. However, this improvement was noticed to be more among glargine group.

One of the most important issues, which may be neglected by many of health care providers, is pre-Ramadan education. Face to face education was done to all of participants in the study. In Addition, we telephoned them every 10 days to answer their questions and give them instructions to ensure safe fasting as this is noticed to be extremely beneficial in passing Ramadan fasting without any hazards [12].

Unfortunately, there is a paucity of research data and trials that investigate Ramadan fasting among elderly, this makes providing specific recommendations is hard. DAR guidelines recommend careful evaluation for elderly patients with T2D who are willing to fast Ramadan and risk of hypoglycemia should be minimized by using protocols with minimal or lower risk of hypoglycemia as elderly patients are vulnerable to develop hypoglycemia more than younger patients [3].

Among the conducted study, it was noticed that NPH group has numerically lower hypoglycemic episodes in comparison to glargine group (3 versus 8 episodes respectively). Moreover, days to break fasting due to hypoglycemia are statistically significantly lower in NPH group (3 days versus 10 days among Glargine group). On the other hand, no difference is noticed regarding days to break fasting due to hyperglycemia between 2 groups (3 days in both groups). **Bakiner *et al.*** [13] observed in their trial that conducted in Turkey in 2009 that there is no difference regarding hypoglycemic episodes between patients using glargine U100 in Ramadan -with dose modification- in comparison to those non fasting. To the best of our knowledge, we did

not find any trial that compare NPH versus Glargine U100 in Ramadan fasting among general population nor in elderly. Also, we haven't met certain trial to investigate the usage of NPH -in basal oral protocol- among elderly fasting Ramadan.

Some authors recommend shifting to insulin analogues during Ramadan to minimize hypoglycemia, this may with usage of prandial analogues which is associated with lower incidence of hypoglycemia in comparison to human insulin [14], but in our study we found that NPH has lower incidence of hypoglycemia, this may be attributed to its shorter duration of action in comparison to Glargine U100 which makes the NPH level in the nadir in the hours before iftar if taken as in our study.

Regarding the cost which is an important issue in managing patients with T2DM especially elderly, we found that we can achieve more safe fasting with lower cost while using NPH in comparison to Glargine U100. The mean daily dose of basal insulin among participants per day is about 30 units. This means that each patient needs about 3 cartridges per month (i.e., 96 Egyptian pounds for NPH versus 387 Egyptian pounds for glargine).

Lastly, the NPH group ended Ramadan with a slightly higher HbA1c in comparison to Glargine group (7.79 gm% versus 7.57 gm%). Although this difference has shown statistical difference, but 0.2 gm% for few weeks may not be harmful for that category of patients. The psychological and medical advantages from completing Ramadan fasting with lower hypoglycemic episodes and days to break fasting are thought to be more beneficial to elderly patients. Nevertheless, prolonged studies should focus on this point particularly to see the long-term effect on HbA1c.

CONCLUSION

In conclusion, among elderly patients fasting Ramadan with basal oral regimen, using NPH may be suitable cheap and widely available basal insulin in comparison to Glargine U 100, with a lower episode of hypoglycemia that making the patient break his fasting. Nevertheless, it should be noted that among patients using NPH there is slight increase in their HbA1c after Ramadan. Further studies are needed on large scale of patients and for longer duration of follow up to confirm the continuity of this hyperglycemia and its effects on patients' glycaemic profile and its cost effectiveness.

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