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The Effect of Regular Human Insulin and Glulisine Insulin on Blood Glucosa Concentration in Diabetic Nephropathy Patients with Hyperglycemia

[1*]Budi Suprapti, [2]Agung Pranoto, [1]Ardian Avrilena Mp., [1]Sumarno, [1]Samirah, [1]Wenny Putri Nilamsari

[1]*Clinical Pharmacy Department, Faculty of Pharmacy Airlangga University Surabaya Indonesia,* [2]*Internal Medicine Department, Dr.Soetomo Hospital, Surabaya Indonesia*

Research Article

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Corresponding Author:
Dr. Budi Suprapti, Apt., MSi
Clinical Pharmacy Department
Faculty of Pharmacy Airlangga University
Campus B Jl. Darmawangsa Dalam, Surabaya, Indonesia
Office phone: +62-031-5033710
Fax number: +62-031-5020514
Mobile: +62-08155086694
Email: budiprapti@yahoo.co.id

Abstract

Objectives: This study was done to compare the effect of RHI 15 minutes before meal and glulisine insulin on blood glucose (BG) achievement and frequency of hypoglycemia in hospitalized Diabetic Nephropathy (DN) patients with hyperglycemia.

Method: Subjects were hospitalized DN patient with inclusion criteria: man/woman with DN stage 3-5 with or without hemodyalisis, 18-65 year old, BMI 18-35 kg/m2, glucose concentration within 200-400 mg/dl, provide written informed consent. Subject randomly divided into RHI and glulisine group. RHI was given 15 minutes before meal and glulisine insulin given 2 minutes before meal. Every subject was examined for preprandial BG (morning, afternoon, and night), 2 hour postprandial BG (morning, afternoon, and night) and bedtime BG concentration for three sequential observation, 24 hours each. Analysis BG data was done to see BG target achievement based on American Diabetes Association (ADA) target.

Result: From the total samples 30 patients (RHI: n = 15; insulin glulisine: n = 15) the results showed that on 1st observation, preprandial, 2 hour post prandial, and bedtime BG had not reached ADA target. However, on the 2nd and 3rd observation, 2hpp blood glucose of both group had reached ADA target, but preprandial and bedtime still had not reached ADA target, the achievement less than 50% patients. The target achievement of preprandial, 2hPP and bedtime BG between RHI and glulisine insulin group was not significantly different. During study, there was no incidence or risk of hypoglycemia in both groups.

Conclusion: There was not significantly different in preprandial, 2hPP and bedtime glucose achievement between group RHI 15 minutes before meal and group glulisine insulin.There was no incidence or risk of hypoglycemia in both groups.

Keywords: *Diabetes Mellitus, Diabetic Nephropathy, Regular Human Insulin, Glulisine Insuline, Blood Glucose, Hypoglycemia*

Introduction

Diabetic nephropathy (DN) is a kidney disorder such as the condition of kidney failure caused by diabetes mellitus (DM). DN is defined as a clinical syndrome characterized by persistent albuminuria (> 300 mg/24 hours or> 200 mcg / min) at least in two measurements within 3-6 months [1, 2]. DN clinical criteria are defined if there are persistent albuminuria, duration of diabetes more than 10 years, suffering from DN without any disease in the kidney and renal tract. DN is associated with increase of blood pressure and decrease of glomerular filtration rate (GFR) [3].

Glycemic control is the most important management to prevent and treat DN. Glycemic control also reduces the risk of macrovascular and microvascular complications in other organs. Poor glycemic control will accelerate loss of renal function in DN [4].

Decrease of renal excretion causing DN patients are contraindicated a lot of oral antidiabetic (OAD) or they require dose adjustment [5]. It also causes decrease of insulinase which will extend the half-life of insulin, thereby increase insulin concentration in the systemic circulation and then causes the DN patients at greater risk of hypoglycemia. Therefore, dose titration using insulin is easier than using OAD, particularly insulin bolus given at mealtime (prandial insulin) [6]. Among all types of insulin, regular human insulin (RHI) and insulin glulisine are most often used.

Most of RHI is in hexamer complexes (6 insulin molecules) and in smaller proportion as monomers and dimers. When injected subcutaneously, RHI needs a lot of time to dissociate into dimers and monomers before it is absorbed into the systemic circulation, therefore RHI has onset of action around 30 to 60 minutes. RHI reach peak concentration at 2.5 to 5 hours after administration and has duration of action 6-8 hours. All of those pharmacokinetic profiles make RHI need at least 30-60 minutes to work. In addition, RHI may cause post-prandial hyperglycemia and then followed by hypoglycemia if there is no meal at 3-4 hours after subcutaneous injection [7, 8, 9, 10].
At Dr. Soetomo Hospital RHI has been given to patients 15-30 minutes before meal. Giving RHI 30 minutes before eating will prevent increase of postprandial glucose concentration. While, if it is injected 15 minutes before meal, it will lead to postprandial hyperglycemia since onset of action has not been achieved. and will cause hypoglycemia at 4-8 hours after injection of RHI [6,7,11].

Insulin glulisine is an endogenous insulin analogue that is modified by replacing the asparagine into lysine at position B3 and lysine to glutamic acid at position B29 which increases the solubility of insulin glulisine at physiological pH [10,12]. Compared with RHI, glulisine insulin absorption after subcutaneous injection is faster (10-15 minutes) than that of RHI. Moreover, peak effect of glulisine insulin is reached more quickly (<1 hour) and duration of action is shorter (4-6 hours) than those of RHI [10, 13]. Pharmacokinetic profile of glulisine insulin is more similar to physiological insulin than those of RHI. In addition, the onset of action of insulin glulisine which is faster than that of RHI will make patients more convenient since they shouldn't wait for 60 minutes before taking meal [10, 14, 15]. The duration of action of glulisine insulin is about 4 hours and it is not dose-dependent, while RHI has longer duration of action when given in larger doses. Thereby, glulisine insulin is more beneficial than RHI as glulisine insulin has a lower risk of hypoglycemia. Several studies showed that glulisine insulin was as effective as RHI, even there was one study that showed glulisine insulin was more effective than that of RHI in decreasing HbA1c [10].

Based on that background, we will conduct an observational cross-sectional study comparing the effect of RHI given 15 minutes and glulisine insulin given 2 minutes before meal on blood glucose concentration and frequency of hypoglycemia in hospitalized DN patients with hyperglycemia.

Material and Method

This study was randomized control trial to compare BG concentration and target achievement of RHI and glulisine insulin in hospitalized ND patients with hyperglycemia at Internal Medicine Department, Dr. Soetomo Hospital, Surabaya Indonesia and the research design was approved by Ethic Committee. Inclusion criteria were man/woman with DN stage 3-5 with or without hemodyalisis, 18-65 years old, BMI 18-35 kg/m2, glucose concentration within 200-400 mg/dl, provide written informed consent. Patients who have other comorbids (for instance: stroke, chronic heart failure, acute myocardial infarction (AMI)) hiperosmolar, ketoacidosis diabetic, sepsis, pregnant) are excluded. Dropped out criteria were patients who die or decide to finish therapy before 3 sequential observation, suffer from severe hypoglycemia causing withdrawal of insulin, suffer from hypersensitive, and decide to resign from study.

Subject randomly divided into RHI and glulisine group. RHI was given 15 minutes before meal and glulisine insulin given 2 minutes before meal. Insulin dose given was adjusted in accordance with CBG level. Patients who have CBG level in the range 200-300 mg / dL received maintenance dose 3x4 UI daily, while patients in the range of 300-400 mg / dL received 3x6 UI daily. In the time course of observation, insulin dose will be adjusted, dose escalation performed if the patient does not respond to previous insulin dose, whereas dose reduction was done if patients blood glucose had achieved the target and to avoid the risk of hypoglycemia. Every subject was examined for preprandial BG (morning, afternoon, and night), 2 hour postprandial BG (morning, afternoon, and night) and bedtime BG concentration for three sequential observation, 24 hours each. Blood glucose was assayed by glucostick.

Analysis was done to compare (1) target glucose achievement recommended by ADA including preprandial, 2 hour postprandial and bedtime between group receiving glulisine insulin 2 minutes before meal and group receiving RHI 15 minutes before meal, (2) the incidence of hypoglycemia and hypoglycemia risk between groups.

Results

There were 32 patients meeting the inclusion criteria obtained (RHI: n = 16; insulin glulisine: n = 16) but two patients drop out (one patient in RHI group because of hematemesis that caused hypoglycemia; one patients in insulin glulisine group because of the forced discharge/suboptimal discharge). Therefore, total samples were 30 patients (RHI: n = 15; insulin glulisine: n = 15). Patient demographic data of both groups are relatively similar either in age, BMI and the degree of ND (Table 1).
At admission, casual blood glucose (CBG) level (Table 2) was examined. Besides being used to determine the maintenance dose of insulin, the initial casual plasma glucose (CBG) levels were also analyzed to see the homogeneity of the distribution of the initial CBG levels between groups to avoid bias. Test of independent sample t-test showed no

significant difference in the distribution of initial CBG level between groups (p = 0.590).

Table 1 Patient demographic data of RHI group and glulisine insulin group

Demographic data	RHI Group n = 15 Number of Patients (%)	Glulisine insulin group n = 15 Number of Patients (%)
Sex		
• Male	5 (33.33)	6 (40,00)
• Female	10 (66.67)	9 (60,00)
Age		
• 30–39 year	0	1 (6.66)
• 40–49 year	6 (40,00)	4 (26.67)
• 50–59 year	6 (40,00)	6 (40,00)
• 60–65 year	1 (20,00)	4 (26.67)
BMI (kg/m^2)		
• 18–20	0	1 (6.67)
• 20–25	14 (93.33)	11 (73.33)
• 25–30	1 (6.67)	3 (20,00)
Staging		
• DN III	3 (20,00)	4 (26.67)
• DN IV	5 (33.33)	5 (33.33)
• DN V	7(46.67)	5 (40,00)

Three series of BG observations were revealed in observations 1, 2, and 3. Mean Blood Glucose (BG) for preprandial, postprandial and bed time in RHI and Glulisine insulin group at observation 1, 2 and 3 with its statistic analysis listed in Table 3

Table 2 Initial casual blood glucosa (CBG) level at admission in RHI group and Glulisine insulin group

Initial CBG level	RHI Group (n = 15) Number of Patients (%)	Glulisine insulin group (n = 15) Number of Patients (%)
200–219	4 (26.67)	4 (26.67)
220–239	3 (20,00)	1 (6.67)
240–259	6 (40,00)	5 (33.33)
260–279	2 (13.33)	4 (26.67)
>280	1 (6,67)	1 (6,67)
Mean initial CBG level	244.87 ± 24.77	87 ± 34.67

Table 4 shows comparison target achievement between 2hPP BG morning, noon and night on the observation 1,2 and 3 and its statistical analysis (chi square) for inter - intra group of RHI and glulisine. Comparison target achievement of preprandial and bed time BG in RHI group and glulisine group listed in Table 5 and 6, respectively.

Discussion

In this study RHI and glulisine insulin were administered by subcutaneous injection, were carried out entirely on the arm to avoid the variability of insulin absorption from the injection site. Subcutaneous injection in the arm gives the moderately absorption rate, slower than the abdomen, but faster than the hips and thighs [10, 16].

Mean Blood Glucose (BG) in RHI and Glulisine insulin groups at observation 1, 2 and 3

Table 3: Mean Blood Glucose (BG) in RHI and Glulisine insulin grou observation 1, 2 and 3

	Blood Glucose (mg/dL)		
	RHI Group	Glulisine Group	P
OBSERVATION 1			
Morning preprandial BG	176,50 ± 28,85	165,10 ± 41,69	0,486
Morning 2hPP BG	182,08 ± 36,64	188,00 ± 63,30	0,771
Noon preprandial BG	178,56 ± 43,94	166,83 ± 41,63	0,614
Noon 2hPP BG	174,13 ± 51,73	205,71 ± 54,30	0,120
Night preprandial BG	187,27 ± 37,43	198,15 ± 56,99	0,594
Night 2hPP BG	191,13 ± 46,10	197,60 ± 59,73	0,742
Bedtime BG	181,73 ± 43,60	187,87 ± 59,64	0,750
OBSERVATION 2			
Morning preprandial BG	158,67 ± 44,34	140,73 ± 21,53	0,170
Morning 2hPP BG	147,80 ± 35,86	142,20 ± 20,34	0,603
Noon preprandial BG	162,67 ± 26,02	153,27 ± 20,20	0,279
Noon 2hPP BG	156,40 ± 33,32	153,20 ± 27,27	0,776
Night preprandial BG	160,93 ± 37,51	153,67 ± 34,33	0,584
Night 2hPP BG	131,47 ± 37,32	158,14 ± 27,34	0,045
Bedtime BG	137,79 ± 28,25	156,50 ± 27,50	0,087
OBSERVATION 3			
Morning preprandial BG	151,40 ± 30,61	154,13 ± 14,58	0,757
Morning 2hPP BG	141,53 ± 27,90	144,80 ± 18,56	0,709
Noon preprandial BG	144,67 ± 33,50	146,07 ± 20,28	0,891
Noon 2hPP BG	142,57 ± 25,22	136,87 ± 27,03	0,462
Night preprandial BG	141,33 ± 32,48	149,20 ± 20,32	0,433
Night 2hPP BG	141,54 ± 32,09	136,93 ± 21,31	0,654
Bedtime BG	147,54 ± 25,79	141,33 ± 19,89	0,479

Insulin used in patients with DN are expected to control the 2hPPG, preprandial glucose, and bedtime glucose without causing hypoglycemia. Based on ADA, desired target levels of 2hPPG range from 70-179 mg/dL and target of preprandial and bed time glucose level range from 70-130 mg/dL [17].

Table 4 Comparison achievement 2hPP glucose level in RHI group and glulisine insulin groups

Observation	Time	% target 2hPP glucose(*)		p value		
		RHI (%)	Glulisine (%)	Intergroup	Intra group RHI	Glulisine
1	Morning	46,15	50,00	0,842		
	Noon	46,67	35,71	0,461	0,589	0,734
	Night	33,33	40,00	0,705		
	Total	**42,05**	**41,90**	**0,600**		
2	Morning	86,67	100,00	0,143		
	Noon	66,67	93,33	0,068	0,355	0,581
	Night	80,00	92,86	0,512		
	Total	**77,78**	**95,40**	**0,048**		
3	Morning	93,33	100,00	0,309		
	Noon	100,00	100,00		0,411	0,360
	Night	100,00	93,33	0,343		
	Total	**97,78**	**97,78**	**0,947**		
Total 2hPP glucose(**)		**72,54**	**78,36**	**0,367**		

(*) % target achievement 2hPP glucose obtained from the number of patients who achieved the target divided by the number of patients each observation

(**) % target achievement 2hPP total obtained from total patients who achieved the target divided by total observation (1,2,3)

Table 5 Comparison achievement preprandial glucose in RHI group and glulisine insulin group

Observation	time	%target preprandial glucose(*)		P value		
		RHI (%)	Glulisine (%)	Intergroup	Intra group RHI	Glulisine
1	morning	0	20,00	0,136		
	noon	11,110	33,330	0,292	0,299	0,115
	night					
	Total	**3,33**	**13,79**	**0,149**		
2	morning	33,33	26,67	0,690		
	noon	6,67	13,33	0,543	0,189	0,659
	night	20,00	20,00	1,000		
	Total	**20,00**	**20,00**	**1,000**		
3	morning	26,67	0	0,032		
	noon	26,67	20,00	0,666	0,724	0,146
	night	26,67	6,67	0,177		
	Total	**26,67**	**8,89**	**0,047**		
Total preprandial glucose(**)		**18,33**	**14,29**	**0,414**		

(*) % target achievement preprandial glucose obtained from the number of patients who achieved the target divided by the number of patients each observation

(**) % target achievement 2hPP total obtained from total patients who achieved the target divided by total observation

Observation 1 results (Table 3) shows that only noon 2hpp mean BG levels of the RHI group reached the ADA target. There were no significant differences in morning, noon and night of preprandial, 2hpp and bedtime glucose level between insulin glulisine and RHI groups (p> 0.05). While observation 2 shows morning, noon, and night 2hpp mean BG levels both groups had reached the target. In contrast to 2hpp levels, mean of preprandial BG for all time and bedtime BG levels both groups did not reach the target. At observation 3 morning, noon and night 2hpp mean BG levels both groups reached the ADA target, but the mean levels of all preprandial BG levels both groups did not reach the target. There was no significantly difference of all glucose types (morning, noon and night 2hpp, preprandial, and bedtime BG) between RHI and insulin glulisine group (p> 0.05).

Table 6 Comparison bedtime level in RHI group and sine insulin group

Observation	Target bedtime glucose(*)		chi square
	RHI (%)	Glulisine (%)	
1	13.33	20,0	0,624
2	35,70	14,29	0,424
3	30,77	26,67	0,811
Total (**)	**26,29**	**20.45**	**0,529**

(*) % target achievement bedtime glucose obtained from the number of patients who achieved the target divided by the number of patients each observation

(**) % target achievement bedtime total obtained from total patients who achieved the target divided by total observation

Table 4 shows comparison target achievement between 2hPP morning, noon and night on the observation 1,2 and 3 and its statistical analysis (chi square). There was an increase in the percentage of patients, observation 1 -3, who achieved the target. The percentage of total patients who achieved 2hpp target at observations 1, 2, and 3 for the RHI group.was 42.05%, 77.78% and 97.78% respectively, while, the insulin glulisine group were 41.90%, 95.40% and 97.78% respectively.

The percentage of patients who achieved 2hpp target at observation 1 was not significantly different in both groups (p = 0.600). At observation 2, the percentage of patients who achieved 2hpp target in the insulin glulisine group was higher than RHI group which were 95.40% vs. 77.78% (p = 0.048) and had similar achievement (97.78%) at observations 3 (p = 0.947).

Several studies showed that glulisine insulin is as effective as RHI, even there is one study that showed glulisine insulin is more effective in

decreasing HbA1c levels [9, 10, 15]. Comparative clinical study of efficacy and safety of insulin glulisine and RHI (both combined with NPH insulin) conducted in patients with type 2 diabetes for 26 weeks showed there was a higher decrease in HbA1c levels in the glulisine insulin group than RHI group. That study also shows the results of self-monitoring blood glucose (SMBG) at 7 points which was lower in the glulisine insulin group than RHI group [11]. Results obtained from this study also showed that the 2hpp achievement in glulisine insulin group was better than RHI group, especially at observation 2, although not significantly different (p> 0.05).

RHI is in hexamer complex, thus when injected subcutaneously, RHI takes time for dissociating into dimers and monomers before it is absorbed into the systemic circulation, whereas insulin glulisine has been in monomer form. This slow dissociation of RHI causes slower absorption compared to insulin glulisine (30 min vs. 15 min) and when administered subcutaneously, RHI achieves peak time slower than insulin glulisine (2.5 - 5 hours vs. <1 hour). Thus. at 2 hour post meal, RHI has not reached the peak of action, resulting in postprandial hyperglycemia. That factor causes insulin glulisine is able to control postprandial glucose levels better than RHI [8, 9, 10].

Based on ADA, target of preprandial glucose level range from 70-130 mg / dL. The results (Table 5) shows at observation 1, insulin glulisine group reached the percentage of preprandial target higher than RHI group which were 17.78% vs. 3.70% (p = 0.249) respectively. But at observations 2 both group had similar achievement and at observation 3, group of insulin glulisine reached the percentage of reprandial target lower than RHI group which were 8.89% vs. 26,67 (p = 0.047). Overall, the percentage of preprandial glucose target was still low (less than 50%) and there was no significant difference between groups RHI and insulin glulisine group at observations 1, 2, and 3 (p = 0.414).

Bedtime glucose target in this study is the same as ADA recommendations, which range from 70-130 mg/dL. Table 5 showed at observation 1 group glulisine insulin reached the percentage of bedtime target higher than RHI group which were 20% vs. 13.33% (p = 0.624), respectively. However, at observations 2 and 3, group insulin glulisine reached the percentage of preprandial target lower than RHI group which were 14.29% vs. 35.7% (at observation 2) (p = 0.424) and 26.67% vs. 30.77% (at the observations 3) (p = 0.811). Overall there was no significant difference between RHI group and insulin glulisine group at observations 1, 2, and 3 (p = 0.529).

The duration of action of glulisine insulin is shorter than that of RHI (4-5 hours vs. 6-8 hours), no dose-dependent [8, 9, 10]. This factor explain why insulin glulisine group achieved preprandial and bedtime glucose target lower than RHI did, although not significantly different (p> 0.05).

In this study frequency of hypoglycemia and the risk of hypoglycemia were observed. Patients at risk of hypoglycemia if preprandial glucose, 2hpp, and bedtime glucose between 60-69 mg/dL. RHI is stated to have a greater risk of hypoglycemia because RHI has a peak time (2-5 hours) and a longer duration (6-8 hours) than glulisine insulin especially if patients do not take meal 3-4 hours after subcutaneous injection [8,9,10].

The results showed, during study, there was no incidence of hypoglycemia or hypoglycemia risk in both groups. This research was conducted without the use of basal insulin. As discussed previously, there were poor achievements in the preprandial and bedtime BG levels in RHI group which were 18,33% and 26,29% respectively and in glulisine insulin group 14,29% and 20,45% respectively.The administration of bolus insulin (RHI or glulisine) was able to achieved 2hpp target according to ADA, but not for preprandial and bedtime glucose level. Therefore, it is recommended to add basal insulin in the management of therapy.

Conclusion

There was not significantly different in preprandial, 2hPP and bedtime glucose achievement between RHI group and glulisine insulin group, but with poor target achievement of preprandial and bedtime in both groups (less than 50%).There was no incidence of hypoglycemia or hypoglycemia risk in both groups.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

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