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Safety and Efficacy of Di-Peptidyl Peptidase-4 Inhibitors in The Management of Inpatient Elderly with Type 2 Diabetes

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ABSTRACT

Background: Hyperglycaemia in hospitalized elderlies with Type 2 Diabetes (T2D) is frequently seen and increases rates of hospital stay, morbidity and mortality. Basal Bolus Regimen (BBR) is the corner stone in management of hyperglycaemia among non-critically ill hospitalized patients. However, it is complex regimen and associated with increased episodes of hypoglycaemia.

Objective: This study was conducted to explore the efficacy and safety of Di-Peptidyl Peptidase -4 inhibitors (DPP-4i) with or without basal insulin for management of T2D among inpatient hospitalized elderly.

Patients and methods: We included 90 patients with T2D, both males and females, aged 60 years or more. Participants were divided into 3 subgroups; *Group 1* on BBR using glargine U100 and regular insulin, *Group 2* on basal oral regimen using glargine U100 and vildagliptin, and *Group 3* on vildagliptin only.

Results: Of all participants, 68 patients were females, and the mean age of the patients was 68.98 (SD 6.7) years. Mean pre-hospital glycated haemoglobin was 8.09 (SD 1.04) gm%. Documented and severe hypoglycaemia and hospital stay were significantly lower among groups 2 and 3. No serious adverse events reported among all participants.

Conclusion: Using DPP-4i with or without basal insulin is safe, effective, less complex regimen associated with lower episodes of documented and severe hypoglycaemia and hospital stay among elderly patients with T2D.

Keywords: Elderly, Type 2 Diabetes, Inpatient, DPP-4 inhibitors.

INTRODUCTION

Hyperglycaemia among non-critically ill hospitalized patients was reported to be about 22%-46% [1]. Moreover, many cross-sectional studies have reported an estimated prevalence of diabetes in elderly aged (65–75 years) and above 80 years about 20% and 40% respectively [2,3]. Hospitalized elderlies when compared to individuals less than 65 years of age, hospital discharge rates related to diabetes among them are about 2 folds higher [1]. With increased age, with or without presence of diabetes, rates of hospitalization 3.1 times higher among patients with diabetes compared to those who has no history of diabetes [4].

Several clinical trials have been conducted in critically ill patients and have reported that improved glycaemic control reduces length of hospital stay, risk of multi-organ failure and systemic infections. In addition, short term and long-term mortality rates were also decreased among patients with diabetes if blood sugar is well controlled [5-7].

The commonest cause of hospitalization in elderly was related to circulatory disorders, it was estimated that they represent about 28.4% of all hospital stays for elderly. Respiratory disorders were the second most common cause, representing about 14.9%. Musculoskeletal and digestive disorders about 10.8% and 10.7%, respectively. Patients with nervous system disorders accounted for 8% of all hospitalizations within this population. Three other categories each resulted in 3-5% of all hospital stays in the elderly: genitourinary disorders, endocrine disorders, and infections [6].

Plenty of professional societies have recommended insulin therapy as the cornerstone for the inpatient management of hyperglycaemia [8]. Nevertheless, insulin regimens -mainly multiple daily injections or Basal Bolus regimen (BBR) were associated with increased risk of hypoglycaemia and complexity of the regimen for health care providers [9].

So, simple regimens with similar glycaemic efficacy to BBR and less episodes of hypoglycaemia are needed to improve the care for non-critically ill patients with diabetes. Data from some Randomized Controlled Trials (RCT) conducted among non-critically ill patients with diabetes have reported that treatment with a Di-Peptidyl Peptidase-4 inhibitors (DPP-4i) alone or in combination with basal insulin results in similar glycaemic control with less risk of hypoglycaemia than BBR [6,10].

DPP-4i are attractive drugs to be used as they act by stimulating insulin and inhibiting glucagon - in a glucose dependent manner- with low risk to develop attacks of hypoglycaemia. Furthermore, they are weight neutral and don't produce hemodynamic changes like Sodium Glucose Co-Transporter 2 inhibitors (SGLT2i) and they have no risk to develop euglycemic ketosis [11].

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Use of Oral Antidiabetic Drugs (OAD) has not been recommended in older clinical guidelines for management of hyperglycaemia among hospitalized patients [12- 13], due to limited data and paucity of RCT about safety and efficacy of OAD drugs and potential unwanted side effects of older agents like metformin, sulfonylureas and thiazolidinediones [14]. However, few years ago, some RCT have conducted to assess the safety and efficacy of DPP4-i in general medicine and surgical patients with Type 2 Diabetes (T2D) and have shown good safety and efficacy [6,10,15,16].

To the best of our knowledge, no study was conducted to assess the safety and effectiveness of using DPP-4i -with or without basal insulin- among elderly hospitalized patients with T2D. Also, we haven't found similar study conducted to test the use of DPP-4i in Egyptian hospitalized patients with T2D.

PATIENTS AND METHODS

This clinical trial was a pilot study, single centre, open labelled, randomized trial carried out on 90 Egyptian elderly patients admitted to diabetes and geriatrics ward in Specialized Medical Hospital, Mansoura University, during the period from January 2022 to September 2022.

We included both males and females with T2D aged 60 years or older after agreeing to participate in the study and known to have T2D at least 3 months before hospitalization and their random blood glucose (RBG) at time of hospitalization was <400 mg/dl. Moreover, only patients on OAD before hospitalization or insulin naïve patients or on low dose insulin (defined as total daily dose <0.4 unit/kg/d) were recruited.

Exclusion criteria were patients with first discovered T2D, other types of diabetes such as late onset Autoimmune Diabetes of Adults (LADA) or Type 1 Diabetes (T1D). In addition, we also excluded patient with severe uncontrolled T2D (RBG $\geq$400 mg/dl) or those requiring high doses of insulin (defined as total daily dose $\geq$0.4U/kg/d). Also, hospitalized patients due to hyperglycemic crisis like diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar crisis (HHS), patient with advanced heart failure (New York Heart Association (NYHA) classification 4), patient with decompensated liver cirrhosis, patient on Ryle feeding or total parenteral nutrition were also excluded. Finally, patients with past history of pancreatitis or family history of medullary thyroid carcinoma and/or multiple endocrine neoplasia (MEN) were excluded.

Comprehensive geriatric assessment was done including thorough history (with stress on duration of diabetes, pre-hospitalization treatment modality, glycaemic control, and presence of other diabetic complications). The following laboratory investigations were ordered: glycated haemoglobin (HbA1c), liver function tests (SGPT, SGOT, INR and serum albumin). Moreover, creatinine was measured and estimated glomerular filtration rate (eGFR) was calculated using the original Modification of Diet in Renal Disease (MDRD) 4 variable equation.

Patients were divided into 3 subgroups; ***Group 1*** on BBR using insulin glargine U 100 and regular Insulin, ***Group 2*** on basal oral regimen (BOR) using glargine U100 and vildagliptin, and ***Group 3*** on Vildagliptin only. In groups with vildagliptin, if eGFR 50 ml/min or more vildagliptin was given twice daily & if less than 50 ml/min it was given once daily. In groups taking basal insulin, 0.1 U/kg/ day was started once daily and gradual titration was done till fasting blood sugar (FBS) was from 100-140 mg/dl.

In group of BBR, 0.4U/kg/d was estimated first, 50% of the total dose was glargine U100, and it was given once daily and gradual titration was done till FBS reach 100-140 mg/dl. The remaining 50% of the total dose was divided on the 3 main meals and pre-prandial blood glucose was measured and corrective doses were added if needed. The following were assessed: days of hospitalization, seven self-monitoring of blood glucose (SMBG) reading (pre and postprandial and bedtime). Moreover, number of documented and/or severe hypoglycemic attacks, number of strips consumed during hospitalization and days of hospitalization were recorded. Glucose variability was assessed using the coefficient of variation (CV). CV was estimated by dividing the standard deviation (SD) on the mean of the previous seven blood glucose readings. According to the international consensus on use of continuous glucose monitoring, stable glucose levels are defined as a CV 36% or less, and unstable glucose levels are defined as CV >36%[17].

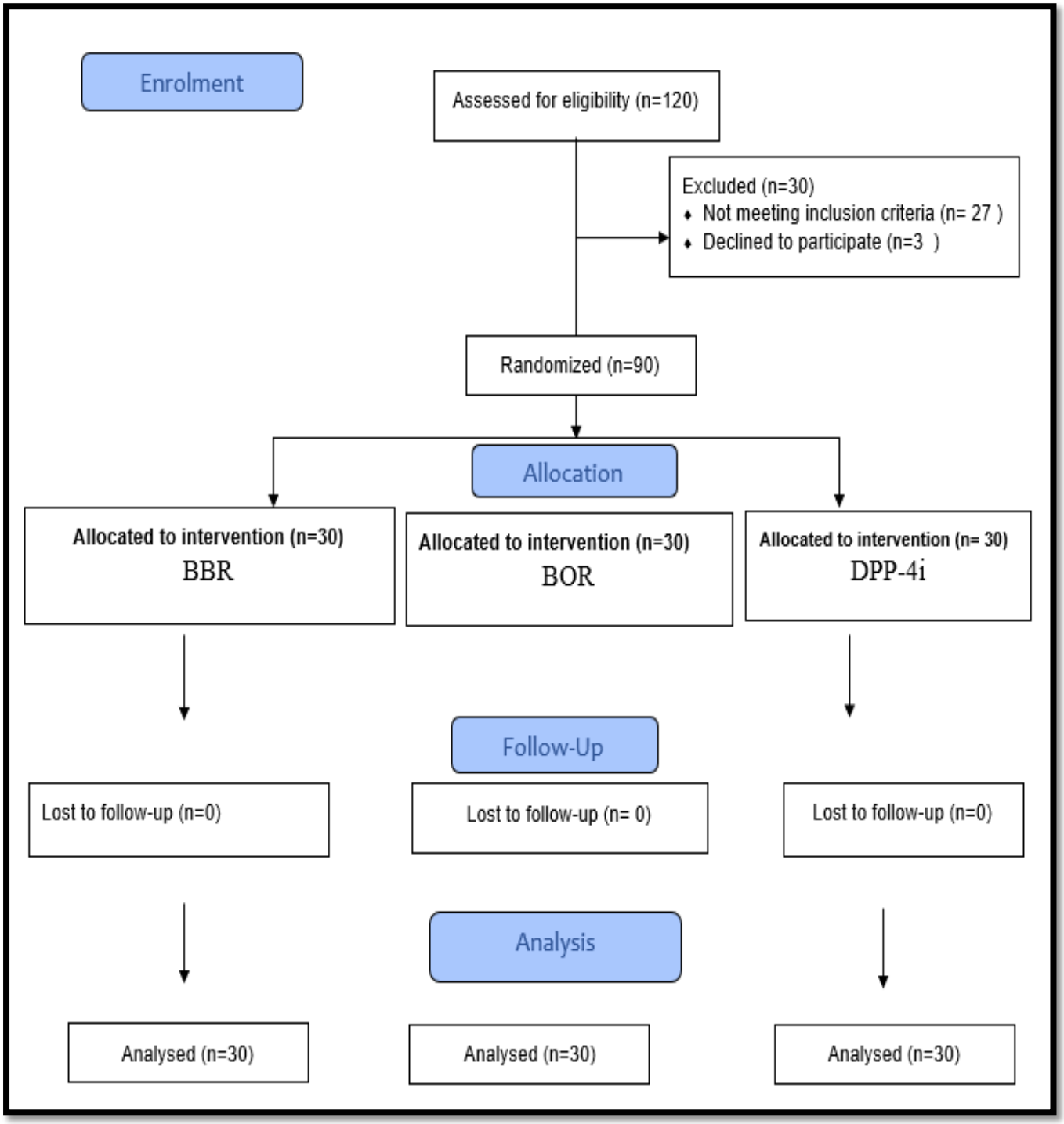

Figure (1): CONSORT flow chart showing study design.

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.21.12.1556). This work has been carried out in accordance w]ith The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analysis was performed by SPSS software, version 28 (SPSS Inc., PASW statistics for windows version 28. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data, and mean and standard deviation (SD) for normally distributed data after testing normality using Kolmogrov-Smirnov test.

Chi-Square Monte Carlo tests were used to compare qualitative data between groups as appropriate. Kruskal-Wallis and One Way ANOVA test were used to compare between 3 studied groups. 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. P value <0.05 was considered significant.

RESULTS

Table 1 shows that there is no significant statistically significant difference between the different groups regarding sociodemographic data.

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

Variable	Group 1 BBR N =30	Group 2 BOR N =30	Group 3 DPP-4i N =30	test of significance	within group significance
Age (Years) (Mean ± SD)	68.63 ± 7.02	69.67 ± 6.47	68.63 ± 7.02	F=0.228 P=0.797	P1=0.560 P2=1.0 P3=0.560
Sex **-Male** **-Female**	 8 (26.7%) 22 (73.3%)	 10 (33.3%) 20 (66.7%)	 4 (13.3%) 26 (86.7%)	 χ^2=3.37 P=0.186	P1=0.573 P2=0.197 P3=0.067
Marital status (%) **-Single** **-Married** **-Widow**	 2 (6.7 %) 16 (53.3%) 12 (40%)	 2 (6.7%) 16 (53.3%) 12 (40%)	 7 (23.3%) 10 (33.3%) 13 (43.3%)	 χ^2=6.30 P=0.177	 P1=1.0 P2=0.122 P3=0.122
Working N (%) **-Yes** **-No**	 5 (16.7%) 25 (83.3%)	 3 (10 %) 27 (90 %)	 2 (6.7 %) 28 (93.3%)	 χ^{2MC}=1.58 P=0.455	P1=0.448 P2=0.228 P3=1.0
Special habits N (%) **-Smoker** **-Non smoker**	 4 (13.3 %) 26 (86.7 %)	 6 (20 %) 24 (80 %)	 2 (6.7%) 28 (93.3%)	 χ^{2MC}=2.31 P=0.315	P1=0.488 P2=0.671 P3=0.129

F: One Way ANOVA test, MC: Monte Carlo test, χ^2=Chi-Square test, P1: Difference between group 1&2, P2: Difference between group 1&3, P3: Difference between group 2&3.

Table 2 Shows that there is no significant statistically significant difference between the different groups regarding associated comorbidities.

Table (2): Comparison of associated comorbidities among the studied groups

Variable	Group 1 BBR n=30	Group 2 BOR n=30	Group 3 DPP-4i n=30	test of significance	within group significance
Hypertension	23 (76.7 %)	21 (70%)	16 (53.3 %)	χ^2=3.90 P=0.142	P1=0.559 P2=0.058 P3=0.184
Atrial Fibrillation	3 (10 %)	1 (3.3%)	0 (0%)	χ^{2MC}=3.66 P=0.160	P1=0.301 P2=0.08 P3=0.313
Diabetic Neuropathy	15 (50 %)	14 (46.7%)	11 (36.7%)	χ^2=3.661.17 P=0.557	P1=0.796 P2=0.297 P3=0.432
Diabetic Retinopathy	7 (23.3 %)	3 (10%)	2 (6.7%)	χ^{2MC}=4.04 P=0.133	P1=0.166 P2=0.071 P3=0.640
Thyroid Diseases	9 (30 %)	5 (16.7 %)	6 (20%)	χ^{2MC}=1.67 P=0.434	P1=0.222 P2=0.371 P3=0.739
Obstructive Sleep Apnoea	1 (3.3 %)	1 (3.3 %)	3 (10%)	χ^{2MC}=1.69 P=0.429	P1=1.0 P2=0.301 P3=0.301
Ischemic Cerebral Stroke	5 (16.7 %)	7 (23.3 %)	3 (10%)	χ^{2MC}=1.92 P=0.383	P1=0.519 P2=0.448 P3=0.166
Ischemic Heart Disease	18 (60 %)	18 (60 %)	11 (36.7%)	χ^2=64.36 P=0.113	P1=1.0 P2=0.120 P3=0.120
Heart failure	19 (63.3)	17 (56.7)	14 (46.7%)	χ^2=1.71 P=0.425	P1=0.792 P2=0.299 P3=0.606
eGFR (ml/min) Mean ± SD	44.87 ± 10.99	50.73 ± 12.3	48.17 ± 11.81	F=1.75 P=0.180	P1=0.307 P2=0.565 P3=0.654

Table 3 shows that there were no statistical significant differences between the 3 groups, regarding the duration of diabetes. However, *Group 1* has the longest duration of T2D in comparison to group 3. Moreover, there is significant difference between the 3 groups regarding HbA1c before hospitalization with highest HbA1c in *Group 1*. One the other hand, no significant difference was found regarding pre-hospital treatment apart from *Group 3* which has the highest number of patients taking metformin.

Table (3): Comparison of duration of T2D, pre-hospital treatment and HbA1c before hospitalization between the studied groups

Variable	Group 1 BBR n=30	Group 2 BOR n=30	Group 3 DPP-4i n=30	test of significance	within group significance
Diabetes duration (years)	12 (3-38)	11 (4-23)	8.5 (3-17)	KW=4.94 P=0.085	P1=0.377 **P2=0.03*** P3=0.171
Treatment N (%)					
Metformin	15 (50 %)	20 (66.7 %)	24 (80%)	χ^{2MC}=6.0 **P=0.05***	P1=0.190 **P2=0.015*** P3=0.243
Sulfonylurea	7 (23.3 %)	13 (43.3%)	13 (43.3%)	χ^{2MC}=3.45 P=0.179	P1=0.100 P2=0.100 P3=1.0
DPP-4 inhibitors	6 (20 %)	7(23.3 %)	12 (40 %)	χ^{2MC}=3.43 P=0.180	P1=0.754 P2=0.091 P3=0.165
Premixed insulin	11 (36.7 %)	5 (16.7 %)	4 (13.3 %)	χ^{2MC}=5.53 P=0.063	P1=0.08 P2=**0.037*** P3=0.718
HBA1C (gm%)	8.36 ± 1.13	8.05 ± 0.89	7.87 ± 1.07	F=3.55 P=**0.03***	P1=0.240 P2=0.068 P3=0.511

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test, P1: Difference between group 1&2, P2: Difference between group 1&3, P3: Difference between group 2&3. *Statistically Significant.

Table 4 shows that there is significant statistical difference between the 3 groups regarding mentioned points. *Group 1* has the longest duration of hospitalization, the more consumed strips, more documented and severe hypoglycaemic episodes. Vice versa was noticed in *Group 3*.

Table (4): Comparison of between the studied groups regarding days of hospitalization, number of consumed strips in SMBG, documented and severe hypoglycemic episodes.

Variable	Group 1 BBR N =30	Group 2 BOR N =30	Group 3 DPP-4i N =30	test of significance	Within group significance
Days of Hospitalization Median (range)	5 (2-10)	3 (2-11)	4 (2-7)	KW=9.86 **P=0.007***	P1=**0.015*** P2=**0.036*** P3=0.680
Number of consumed SMBG strips Median (range)	39.5 (15-82)	23.5 (14-86)	30 (14-50)	KW=13.66 P=**0.001***	P1=0.001* P2=**0.003*** P3=0.156
Documented hypoglycemia Median (range)	3 (0-8)	0 (0-2)	0 (0-2)	KW=41.03 **P<0.001***	P1<**0.001*** P2<**0.001*** P3=**0.036***
Severe hypoglycemia Median (range)	0 (0-4)	0 (0-4)	0 (0-0)	KW=7.59 P=**0.023***	P1=0.766 P2=**0.005*** P3=**0.01***

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test P1: Difference between group 1&2, P2: Difference between group 1&3, P3: Difference between group 2&3. *Statistically Significant

Table 5 shows no significant statistical difference between the studied groups regarding CV.

Table (5) Comparison of Coefficient of variation between the studied groups.

Variable	Group 1 BBR N =30	Group 2 BOR N =30	Group 3 DPP-4i N =30	test of significance	within group significance
Glucose stability N (%)					
-Stable (CV < 36%)	30 (100 %)	28 (93.3 %)	29 (96.7 %)	MC=2.07	P1=0.492
-Unstable (CV >36 %)	0 (0%)	2 (6.7 %)	1 % (3.3 %)	P=0.355	P2=1.0
					P3=1.0

F: One Way ANOVA test, MC: Monte Carlo test P1: Difference between group 1&2, P2: Difference between group 1&3, P3: Difference between group 2&3.

DISCUSSION

This randomized controlled trial was designed to compare the use of DPP-4i with or without basal insulin to BBR, although BBR is the standard regimen of care for hospitalized non-critically patients. Some clinical trials like RABBIT-2 trial [18], which explored the efficacy of BBR to control hyperglycemia among hospitalized patients with diabetes in medical wards- have shown that only two thirds of patients reached the target (which was defined in the trial as RBG <140 mg/dl). The lack of recommendations to use OAD in hospitalized patients with T2D comes from paucity of data about the safety of some oral drugs, like fear to develop lactic acidosis with metformin and sustained hypoglycaemia from using sulfonylureas. Moreover, use of thiazolidinediones is associated with salt and water retention and may exacerbate heart failure, regardless its delayed onset of action [1].

In Egypt, there is lack of diabetologists and well-qualified nurses who are familiar with BBR and corrective doses. Unfortunately, a lot of Egyptian hospitals still use sliding scale regimen as an insulin protocol for non-critically ill hospitalized patients because of its simplicity in comparison to BBR, although it is not working well in controlling hyperglycaemia and prohibited by most of clinical societies. So, we tried in this trial to search for another simple and effective protocols alternative to BBR to control hyperglycemia in hospitalized patients with T2D. We included in our study 90 elderly patients (68 of them were female) with mean age of the patients 68.98 (SD 6.7) years. The mean pre-hospital HbA1c was 8.09 (SD 1.04) gm%.

The conducted study has addressed that there is significant statistical difference between the 3 different groups regarding hypoglycemia. *Group 1* (BBR) have the highest number of documents and severe hypoglycemic episodes followed by *Group 2* (BOR). No episode of severe hypoglycemia was reported in group 3 due to the smart action of DPP-4i [11] and absence of insulin in the regimen (which is the main cause of severe hypoglycemia). On the other hand, **Umpierrez *et al.*** [10] and **Pérez-Belmonte *et al.*** [19] in their study have reported that no significant difference between BBR, BOR and DPP4i regarding hypoglycaemic episodes. This may be explained by the good knowledge and education of their young physicians and nurses in dealing with BBR and corrective doses. In addition, they used in their study short acting insulin analogues instead of regular human insulin in our study.

Regarding glucose variability, we used CV as a parameter of glucose variability. We estimated it according to the recommendation of international consensus on use of continuous glucose monitoring [17]. Our study doesn't find any statistical difference between the 3 groups regarding CV. In contrast, **Garg *et al.*** [6] compared in their study between saxagliptin versus BBR and they reported that saxagliptin group has significant less glucose variability during hospitalization period. This difference may be explained by the different method of glucose variability assessment. They used continuous glucose monitoring and the hospitalization period was longer than our study.

Finally, we found that patients using vildagliptin with or without basal insulin have shorter hospital stay and a smaller number of consumed strips. This will save a lot of cost in the health care system a developing country like Egypt.

CONCLUSION

Using DPP-4i -with or without basal insulin- among non-critically ill hospitalized elderly patients with T2D seems to be safe and less complex protocol to control hyperglycemia. They are non-inferior regarding glycaemic efficacy when compared to BBR with reduced rates of documented and severe episodes of hypoglycemia. However, larger prospective RCT on wide scale of patients and longer duration are needed.

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