Comparison of 3 Medicine Groups Used to Control Glycemic and Glycated Hemoglobin Levels in Newly Diagnosed Type 2 Diabetes Patients

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Abstract

AIM: This research aims to compare the effectiveness of three medicines groups in controlling glycemic and glycated hemoglobin (HbA1c) levels in the newly diagnosed diabetes mellitus type 2.

METHODS: One hundred fifty newly diagnosed patients with type 2 diabetes were treated by mono therapy and divided into three groups. Each group of 50 patients was treated by one medicine: Group 1 using Diamicron MR 30 mg (Sulfonylurea) – three capsules per day, Group 2 using metformin 500 mg – 1–3 capsules per day, and Group 3 using Januvia (sitagliptin, dipeptidyl peptidase-4 inhibitor) 100 mg – 1 capsule per day. The evaluation of glucose control was based on fasting plasma glucose and HbA1c concentration and divided into three levels: Excellent, good, and poor. The assessment was carried out after every 3 months of treatment, at 3rd month, 6th month, and 12th month (WHO, 2002).

RESULTS: After treatment 3, 6, and 12 months, glucose level was decreased when compared to before treatment in all three groups ($p_{all} < 0.001$). At the month 6th, the groups treated by sulfonylurea and sitagliptin had lower glucose level than metformin (with p values were 0.04 and 0.01, respectively), and maintained the low glucose level from the month 6th to month 12th (with p values were 0.71 and 0.77, respectively) while glucose level of the metformin group increased (p = 0.005). HbA1c has decreased dramatically in all three groups after treatment (p values of sulfonylurea group at the month 3rd, 6th, and 12th vs. before treatment were 0.006, 0.021, and 0.001, respectively; all p values of metformin group at the month 3rd, 6th, and 12th vs. before treatment were below 0.001; all p values of sitagliptin group at the month 3rd, 6th, and 12th vs. before treatment were below 0.001). The group treated by sitagliptin got the highest ratio of excellent HbA1c control (82% after 12 months of treatment).

CONCLUSION: Significant improvement of glucose and HbA1c levels was observed in all three groups. Glucose control level of group treated with sulfonylurea was markedly improved and the group treated with sitagliptin achieved optimal control of HbA1c.

Introduction

Diabetes mellitus type 2 is a noninfectious chronic disease with tendency for rapid increase in observed numbers of patients worldwide. The metabolic disorder in diabetes mellitus is characterized by high glucose concentration which is caused by absolute or relative insulin deficit. Prolonged hyperglycemia causes functional disorders and failure in many organs especially eyes, kidney, neural system, and vascular system [1].

The treatment target is to control strictly blood glucose concentration, glycated hemoglobin (HbA1c), vascular risk, and lipid disorder. If the HbA1c level is normal, the risk of cardiovascular is decreased [2]. However, about 50% patients with diabetes achieve the target of HbA1c control level after treatment [3].

All the therapy for diabetes achieves the same target. This is necessary for excellent glycemic control to reduce the complications. In recent years, the number of medicines used for treating diabetes has been increased. However, the treating strategy is not only to reduce the original glycemic level but also to maintain over time by many different mechanisms because of high efficacy, decreasing the risk of hypoglycemia, low cost [4].

The latest therapy option for initial monotherapy recommended by the American Diabetes Association and the European Association for the Study of Diabetes was using metformin for newly diagnosed patients [5]. Others medication for lowering such as dipeptidyl peptidase-4 (DPP-4) inhibitors or sulfonylureas nowadays had their later generation (sitagliptin, Diamicron,…) with lower complications and more safety [5], [6], [7], [8].

The main purpose of this study is to evaluate the effect of control in newly diagnosed type 2 diabetes (nT2D) patients treated by metformin, Diamicron, and sitagliptin as monotherapy.

Materials and Methods

Study design and participants

A cross-sectional study was conducted on the nT2D patients in Quang Ninh Province Hospital from 5/2017 to 4/2019. A total of 150 T2D patients were recruited and randomized in an equal ratio into three groups. Eligible participants were all adult and first diagnosed diabetes mellitus type 2 (based on International Diabetes Federation, IDF criteria 2004). All of participants had not been treated by any kinds of drugs that affect to glucose blood such as thiazide diuretic, corticosteroid, and estrogen contraceptive. Exclusion criteria were pregnancy, cancer, nephritis, nephritic syndrome. Each group of patients has been treated by one group of medicine: Group 1: Sulfonylurea (Diamicron 30 mg × 1–3 tablets/day); Group 2: Metformin 500 mg × 1–3 tablets/day; and Group 3: Sitagliptin (Januvia 100 mg × 1 tablet/day).

Measurements

The blood samples were collected at four points of time: Before treatment, after treatment of 3 months, 6 months, and 12 months. The plasma was collected and stored at −20°C to test glucose, HbA1c in Military Hospital 103. Glucose blood level was examined by hexokinase in AU 5800 (Beckman coulter, US) and HbA1c level was examined by HPLC in Premier 902 (Trinity Biotec, US). Based on the guideline of WHO 2002, the guideline of IDF for managing T2D primary care 2017 and guideline of ADA 2020, glycemic control was classified by three levels (excellent ranging from 3.9 to 6.5 mmol/l; good ranging from 6.5 to 7.5 mmol/l, and poor ranging upper than 8 mmol/l) based on fasting glucose plasma and HbA1c percentage was divided into three level (excellent with HbA1c ≤6.5%; good with HbA1c ranging from 6.6% to 7.5%, and poor with HbA1c >7.5%) [9], [10], [11].

Statistic analysis

We used Stata 12.0 statistic software for Windows. The glucose and HbA1c levels were parametric numbers and presented by mean and standard division. We used a t-test to compare the mean of glucose and HbA1c concentration of all groups. The effect of plasma glucose and HbA1c control was presented in percentage. The percentage of each level (excellent, good, and poor) was equaled to the division of the numbers of that level in each group and the total number of patients in a group (50 patients).

Ethical statement

All participants were dispensed with written informed consents, and the study was approved by the Ethical Committee of Military Medical University, Hanoi, Vietnam (No: 68/2017/QĐ-HĐĐĐ date 28 month 4 year 2017). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Results

Characteristics of study participants

The characteristics of study population were described more details in Table 1.

Table 1: Characteristics of patient participants

Variables	Sulfonylurea	Metformin	Sitagliptin
Age, n (%)	50 (100)	50 (100)	50 (100)
20–39 years, n (%)	1 (2)	1 (2)	4 (8)
40–59 years, n (%)	15 (30)	17 (34)	22 (44)
60–79 years, n (%)	32 (64)	30 (60)	23 (46)
≥ 80 years, n (%)	2 (4)	2 (4)	1 (2)
Median	62.26±10.80	64.02±9.97	59.12±10.9
Range	30–81	37–87	34–85
Gender, n (%)			
Male, n (%)	21 (42)	24 (48)	17 (34)
Female, n (%)	29 (58)	27 (52)	33 (66)

Effect of 3 monotherapies in glycemic concentration

Before treatment, mean fasting glucose level of groups treated with sulfonylurea and metformin was not significantly different, the mean glucose level of sitagliptin group was higher than two others groups (p values were 0.026 and 0.0003, respectively), although patients in three groups were randomly chosen.

In all three groups, the glycemic level of all 3 time points after treatment was significantly lower than before treatment (p < 0.001). In the sulfonylurea and sitagliptin groups, the mean glycemic levels got the target at the month 6th, and still maintained to the month 12th (p value of glycemic level of sulfonylurea and sitagliptin at month 6th vs. month 12th was 0.716 and 0.773, respectively). Except the metformin group, at the month of 12th, the mean glycemic level had the increasing trend (p = 0.005) (Table 2).

Table 2: Comparison of effect on glycemic concentration of three groups before and after treatment

Variables	Sulfonylurea group[a]	Metformin group[b]	Sitagliptin group[c]
Before treatment[1]	8.64±1.98	8.39±1.72	10.34±3.16
p-values	p_{ab}=0.364; p_{ac}=0.026; p_{bc}=0.0003		
After 3 months treatment[2]	6.51±0.69	6.53±0.84	6.83±1.45
p-values	p_{ab}=0.907; p_{ac}=0.1717; p_{bc}=0.1803;		
After 6 months treatment[3]	6.45±0.65	6.34±0.59	6.23±0.64
p-values	p_{ab}=0.3745; p_{ac}=0.1116; p_{bc}=0.3565		
After 12 months treatment[4]	6.4±0.92	6.81±1.14	6.26±0.88
p-values	p_{ab}=0.0436; p_{ac}=0.4585; p_{bc}=0.0113		
p-value	p_{12a}=0.000	p_{12b}=0.000	p_{12c}=0.000
	p_{13a}=0.000	p_{13b}=0.000	p_{13c}=0.000
	p_{14a}=0.000	p_{14b}=0.000	p_{14c}=0000
	p_{23a}=0.515	p_{23b}=0.062	p_{23c}=0.048
	p_{24a}=0.458	p_{24b}=0.100	p_{24c}=0.013
	p_{34a}=0.716	p_{34b}=0.0054	p_{34c}=0.7731

*t-test.

Effect of 3 monotherapies in glycemic control

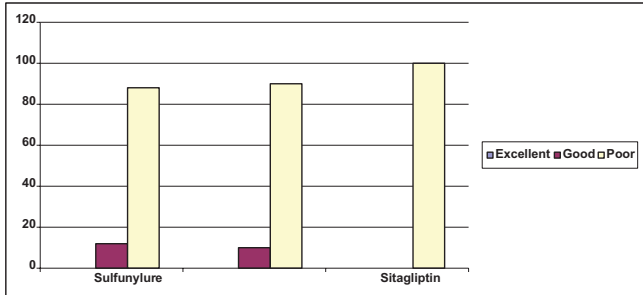Before treatment, most patients had poor glucose control (Figure 1).

Figure 1: The rate of glycemic control of 3 drugs before treatment (%)

After 3 months of treatment, the glucose control at excellent, good, and poor levels is 30%, 54%, and 16%, respectively, in sulfonylurea group; 30%, 50%, and 16% in metformin group, and 22%, 42%, and 36% in sitagliptin group (Figure 2).
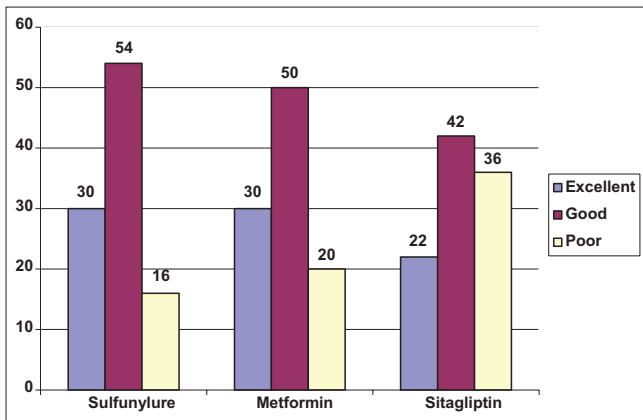

Figure 2: The rate of glycemic control of 3 drugs after treatment 3 months (%)

After 6 months of treatment, the glucose control excellent level of sitagliptin group get the highest rate (48%) and the smallest rate of poor glucose control (8%). Sulfonylurea group had the highest rate of poor glucose control (14%) (Figure 3).
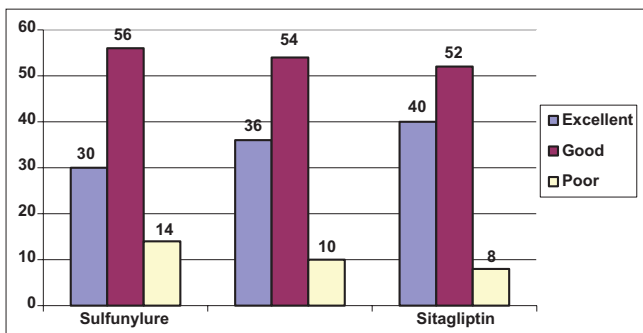

Figure 3: The rate of glycemic control of 3 drugs after treatment 6 months (%)

After 12 months of treatment, sitagliptin group still had the highest rate of glucose control (52%). Metformin group had the highest rate of poor glucose control (36%) (Figure 4).
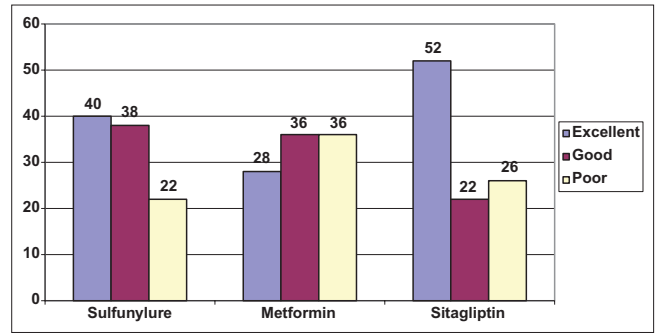

Figure 4: The rate of glycemic control of 3 drugs after treatment 12 months (%)

Effect of 3 monotherapies on HbA1c level

At the starting of the research, HbA1c level of three groups was different ($p_{all} < 0.05$). Sitagliptin group had the highest mean HbA1c (9.1%) (p values of sitagliptin group vs. metformin group and sulfonylurea group were 0.000 and 0.014, respectively).

After treatment, HbA1c level of all three groups was different from before treatment (p values of sulfonylurea group at the month 3rd, 6th, and 12th vs. before treatment were 0.006, 0.021, and 0.001, respectively; all p values of metformin group at the month 3rd, 6th, and 12th vs. before treatment were below 0.001; all p values of sitagliptin group at the month 3rd, 6th, and 12th vs. before treatment were below 0.001).

After treatment 6 months, HbA1c of sitagliptin group was the smallest (p values of sitagliptin group vs. sulfonylurea and metformin groups were 0.007 and 0.001, respectively) (Figure 5).
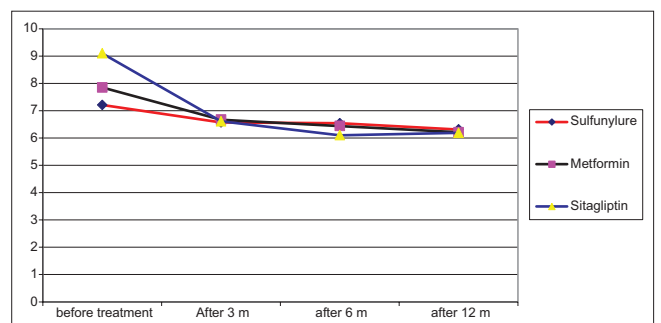
Figure 5: The effect of 3 monotherapies on glycated hemoglobin level before and 3, 6, and 12 months after treatment

Effect of 3 monotherapies on HbA1c control

After treatment of 3, 6, and 12 months, the rates of excellent HbA1c control of all three groups increased. After 12 months, sitagliptin had the highest rate. The rate of poor control of metformin and sitagliptin groups had increasing incident. The control levels of sitagliptin after treatment 6 and 12 months were the bests (80 and 82%) (Table 3).

Table 3: The HbA1c control level before and after treatment

Control level	Sulfonylurea[a]		Metformin[b]		Sitagliptin[c]	
	n	%	n	%	n	%
Before treatment						
Excellent	17	34	0	0	1	2
Good	17	34	25	50	9	18
Poor	16	32	25	50	40	80
After treatment 3 months						
Excellent	23	46	20	40	18	36
Good	19	38	23	46	29	58
Poor	8	16	7	14	3	6
After treatment 6 months						
Excellent	24	48	26	52	40	80
Good	18	36	23	46	10	20
Poor	8	16	1	2	0	0
After treatment 12 months						
Excellent	31	62	36	72	41	82
Good	13	26	11	22	5	10
Poor	6	12	3	6	4	8

HbA1c: Glycated hemoglobin.

Discussion

Regular monitoring blood glucose and HbA1c could not only provide the doctor the data to estimate the effect of lowering medication but also control the results of medication at the best target as recommend to reduce complication. With the newly diagnosed, many evidences had proven that only treating by changing the diet could be inefficient as monotherapy by drug in insulin – independent diabetes patients [12]. Changing the diet can be difficult to get the treatment target. However, when combining with monotherapy, the fasting blood glucose decreased and got the target when followed up to 6 months [13].

When comparing the three medicine groups, the sitagliptin group had the highest proportion of patients who had excellent glucose and HbA1c level after 6 and 12 months. Sitagliptin and the other drugs in the same group had been proved in increasing the effect in glycemic control. Li *et al.* (2014) studied on 207 patients who were treated with metformin with HbA1C concentrations of 7.5–10%, by adding saxagliptin or sitagliptin or vildagliptin into three groups. The results showed that after 24 weeks of treatment, the HbA1c concentrations in these three groups continued to decrease by −1.2%, −1.3%, and −1.1%, respectively [14]. Moreover, sitagliptin stables the DPP-4 substrates, glucagon-like peptide-1, and gastric inhibitory polypeptide, both incretin hormones which act dependently to glucose to stimulate beta cells to secret insulin. Sulfonylurea stimulates directly to beta cells and not depends on glucose. Hence, for the long time, using sitagliptin can reduce stimulating the pancreatic beta cells too much. Moreover, sitagliptin also did not cause gain weight in patients while gain weight and hypoglycemia are side effects of sulfonylurea [15], [16]. Metformin decreases hepatic glucose output. Hermann *et al.* (1994) conducted a study comparing the efficacy of using metformin to sulfonylurea showing that the effects of glucose decrease in blood of metformin and bride are the same and among of them only metformin helped to achieve the glycemic target without gaining weight and hyperinsulinemia [13]. The evidence proved

that metformin significantly reduced the risk of vascular diabetes complications is still absent [17], though the side effect of metformin was rarely. In this study, metformin also had high proportion of excellent glucose and HbA1c control after treatment 12 months.

The study results showed that all three drugs using for type 2 diabetic patients were quite effective for the 1st time; HbA1c concentration decreased, the difference was statistically significant ($p < 0.05$). The HbA1c concentration of three groups at the time of initiation and 3 months after treatment almost achieved the treatment goal according to ADA 2019 (HbA1c< 7%) [18].

Glycemic control is the main method to prevent complications. Criteria to evaluate glycemic control are HbA1c proportion. According to ADA 2019, the goal of glycemic control is HbA1c <7% [18]. HbA1c refers to hemoglobin glycated. Hemoglobin is a protein carrying the oxygen within red blood cell. The binding to glucose in bloodstream is called glycation. While glucose blood may vary from day to day depending on the diet and daily activities, the HbA1c index is constant throughout the life of red blood cells, for about 120 days. HbA1c normal range is 4–6%. Increasing HbA1c by 1% means an increase in glucose blood value of 30 mg/dl (~1.7 mmol/L). The HbA1c test reflects the average glucose blood level over the past 2–3 months. This is the best test helping doctors to monitor and to evaluate glucose blood control. HbA1c >10% indicates the poor control of glucose blood level during the recent period. When HbA1c is <6.5% it indicates excellent glycemic control. If HbA1c is not well controlled, it will significantly increase the risk of diabetes complications. According to Stratton *et al.* (2000), a 1% reduction in HbA1c reduces 21% risk of diabetes (95% confidence interval from 17% to 24%, $p < 0.0001$), 21% for diabetes-related deaths (15–27%, $p < 0.0001$), 14% for myocardial infraction (8–21%, $p < 0.0001$), and 37% for microvascular complications (33–41%, $p < 0.0001$) [19]. Therefore, excellent control of HbA1c is an important goal in the treatment of diabetes and an indispensable criterion to evaluate the effect of a hypoglycemic drug.

The limitation of this research the time that we followed patients was short. So it was difficult to assess the complications because all the patients were newly diagnosed and followed up in only 1 year. Moreover, the complications did not often appear in this period of the disease. Since, the sample had been collected and stored before tested, there could be some imprecision.

Conclusion

Significant improvement of glucose and HbA1c levels was observed in all three groups. Glucose control level of group treated with sulfonylurea was markedly

improved and the group treated with sitagliptin achieved optimal control of HbA1c.

Authors' Contributions

Ngoc Chau Nguyen: Conceptualization, data curation, formal analysis, investigation, project administration, validation, writing – original draft preparation, writing – review & editing; final approval of the version to be published. Quang Thuan Huynh: Conceptualization, data curation, formal analysis, investigation, project administration, writing – original draft preparation, writing – review & editing; corresponding; final approval of the version to be published. Hoai Thuong Pham; Diep Thao Pham; Thi Minh Hoang; Thi Phuong Lan Dam; Thi Hang Ho: Data Curation, investigation, methodology, writing – original draft preparation; final approval of the version to be published. Duy Quy Dang; Nhu Binh Do: Interpretation of data, methodology, writing – original draft preparation; final approval of the version to be published.

Acknowledgments

Ethical Statement

All participants were dispensed with written informed consents, and the study was approved by the Ethical Committee of Military Medical University, Hanoi, Vietnam (No: 68/2017/QĐ-HĐĐĐ date 28 month 4 year 2017). The study was also conducted using good clinical practice following the Declaration of Helsinki.

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