Glipizide combined with metformin versus metformin alone and hypoglycemic seizure: a retrospective cohort study

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To identify the rates of hypoglycemic seizure after receiving glipizide combined with metformin versus metformin alone.

METHODS

We conducted a retrospective cohort study comparing the rate of hypoglycemic seizure in patients after glipizide combined with metformin versus metformin therapy. Patient medical records of those who admitted with hypoglycemia caused by either glipizide combined with metformin or metformin between January 2011 and August 2015 at Khon Kaen Hospital in Thailand. The primary outcome was the rate of hypoglycemic seizure in the patients with the two types of treatment. The secondary outcomes included confusion, lethargy, stupor, coma, metabolic acidosis, and death.

RESULTS

A total of 880 medical records were reviewed (166 in the glipizide combined with metformin group and 126 in the metformin group). There was no differences between the two groups in relation to rate of hypoglycemic seizure; 40 patients (24.1%) in glipizide combined with metformin group and 34 patients (27.0%) in the metformin group (adjusted odds ratio [AOR], 1.75; 95% confidence interval [CI], 0.75 to 4.11). There were also no different in rate of confusion (11.4% vs. 9.5%; AOR, 1.05; 95% CI, 0.36 to 3.01), lethargy (24.1% vs. 19.8%; AOR, 0.90; 95% CI, 0.39 to 2.10), stupor (6.6% vs. 4.0%; AOR, 3.05; 95% CI, 0.55 to 16.81), coma (30.7% vs. 25.4%; AOR, 1.41; 95% CI, 0.86 to 3.11), metabolic acidosis (3.6% vs. 5.6%; AOR, 0.42; 95% CI, 0.08 to 2.20). Two people died; one from each group.

CONCLUSION

In patients with diabetes and hypoglycemia, using glipizide combined with metformin did not increase the rate of hypoglycemic seizure than metformin.

INTRODUCTION

It is estimated that 347 million people worldwide having diabetes.[1] In 2012, diabetes was one of the direct causes of 1.5 million deaths, and most of people with diabetes live in low- and middle-income countries.[1,2] Diabetic patient should control glycemic level by lifestyle modification or medication based on the patient status.[3] Hypoglycemic drugs can cause hypoglycemia, moreover, the hypoglycemic seizure is also a cause for death in 3 to 6% of diabetic patients.[4-7] Glipizide combined with metformin is one of the most prescribed regimen.[8] However, the combination therapy increases risk hypoglycemia more than metformin alone; one systematic review in 2007 based on eight randomized controlled trials, it found that hypoglycemic episodes in patients receiving glipizide were more common than that of metformin.[9] Another case-control study in 2008 conducted in 9,303 in The United Kingdom, with hypoglycemia, it found that use of glipizide was associated with increased risk for hypoglycemia more than that of metformin.[10] However, no published studies have examined the rate of hypoglycemic seizure in patients after receiving glipizide combined with metformin versus metformin alone. The main object of this study was to compare the rates of hypoglycemic seizure after receiving glipizide combined with metformin versus metformin alone.

METHODS

STUDY DESIGN

We conducted a retrospective cohort study comparing the rate of hypoglycemic seizure in patients receiving glipizide combined with metformin versus metformin alone.

PATIENTS RECORDS

We reviewed medical records retrospectively of all patients who admitted with hypoglycemia that was presumably caused by the treatment of either glipizide combined with metformin or metformin by ruling out other causes between January 2011 and August 2015 at Khon Kaen Hospital, Thailand. We excluded the patients with the seizures from intracranial causes such as head injury, stroke or transient cerebral ischemia, with underlying of epilepsy, brain tumor or extracranial cause such as alcohol withdrawal seizure.

EXPOSURE

The exposures in the current study included two groups of oral hypoglycemic agents; the former referred to the group that received glipizide combined with metformin, the latter referred to the group that received metformin therapy only.

OUTCOME MEASURES

The primary outcome was the rate of hypoglycemic seizure in patients after receiving glipizide combined with metformin versus metformin alone. The secondary outcomes included confusion, lethargy, stupor, coma, metabolic acidosis, and death.

DATA COLLECTION

We use the patient database of Khon Kaen Hospital to identify the patients who met our inclusion and exclusion criteria using the International Classification of Disease (ICD) 10 (main or contributory discharge diagnosis ICD-10 code

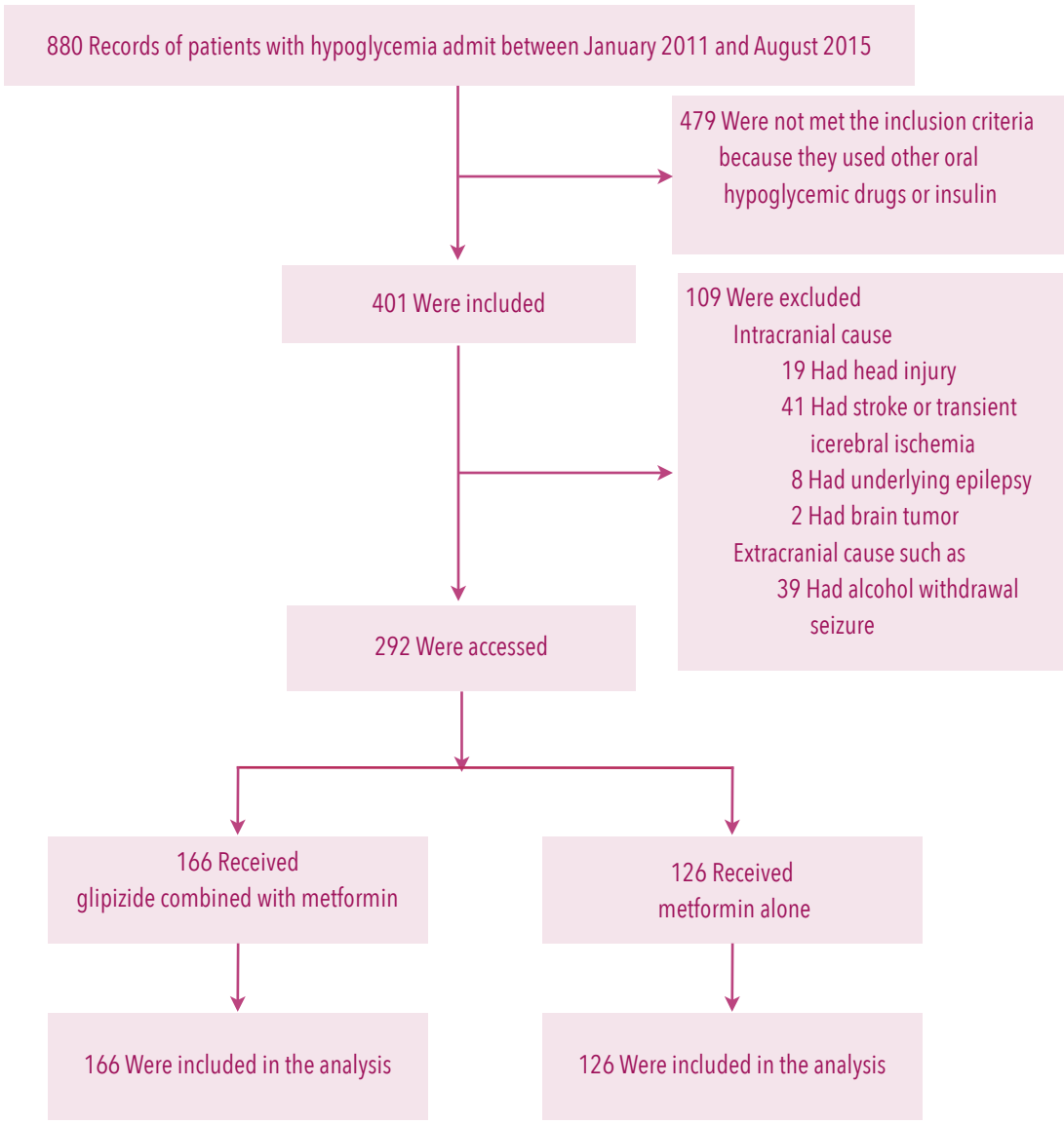

Figure 1. Study flow

E11.01, E16.0, E16.2). For each record, variables including age, sex, hemoglobin A1c, fever (body temperature > 37.8 degree Celsius measured in armpit[20]), shock (lack of blood flow means that the cells and organs do not get enough oxygen and nutrients to function properly on admission)[21], underlying diseases such as hypertension, cirrhosis, chronic kidney disease, malignancy neoplasm, serum creatinine, estimated glomerular filtration rate (GFR), generalized seizure such as tonic-clonic, tonic, clonic, atonic, partial seizure, level of consciousness such as alertness, confusion, lethargy, stupor, coma, metabolic acidosis and death were verified and reviewed.

Table 1. Characteristics of the patients

Characteristic	Glipizide combined with metformin (N=166)	Metformin (N=126)	P Value
Age-yr			0.89
Median	68.4	68.7	
Interquartile range	58.2-76.5	58.7-76.6	
Male sex-no. (%)	61 (36.7)	51 (40.5)	0.516
Hemoglobin A1c-mg%	(n=82)	(n=53)	0.87
Median	6.6	6.9	
Interquartile range	5.8-7.8	6.0-7.7	
Fever-no. (%)	27 (16.3)	26 (20.6)	0.337
Shock-no. (%)	12 (7.2)	18 (14.3)	0.049
Underlying diseases-no. (%)			
Hypertension	112 (67.5)	81 (64.3)	0.569
Cirrhosis	9 (5.4)	5 (4.0)	0.565
Chronic kidney disease	37 (22.3)	30 (23.8)	0.760
Malignant neoplasm	9 (5.4)	6 (4.8)	0.800
Serum creatinine-mg/dl	(n=158)	(n=121)	
Median	1.1	1.2	<0.99
Interquartile range	0.8-1.6	0.8-2.0	
eGFR-ml/min/1.73 m2	(n=158)	(n=121)	0.89
Mean	58.7±31.5	53.3±32.0	

Plus minus values are means ±SD.

STATISTICAL ANALYSIS

The descriptive statistics, categorical variables were described using number and percentage. For continuous variables, all numeric data were tested for their normal distributions using Kolmogorov-Smirnov test, mean and standard deviation (SD) were used if there were normally distributed while median and interquartile range (IQR) were used if there were non-normally distributed. For inferential statistics, chi-square and Fisher's exact test were used in appropriate condition for categorical variable comparison. Student t-test and Mann-Whitney U test were used for normally and non-normally distributed variables respectively. We used relative risk (RR) to analyze the primary outcome, level of consciousness such as alertness,

Table 2. The Primary and secondary outcomes

Outcome	Glipizide combined with metformin (N=166)	Metformin (N=126)	Relative risk with 95% confidence interval
	no. (%)		
Seizure	40 (24.1)	34 (27.0)	0.893 (0.602-1.325)
Generalized	30 (18.1)	21 (16.7)	1.084 (0.653-1.801)
Tonic-clonic	21 (12.7)	8 (6.3)	1.992 (0.913-4.350)
Tonic	6 (3.6)	0	NA
Clonic	2 (1.2)	0	NA
Atonic	1 (0.6)	0	NA
Partial	10 (6.0)	13 (10.3)	0.593 (0.265-1.288)
Level of consciousness			
Alertness	45 (27.1)	52 (41.3)	1.00 (Reference)
Confusion	19 (11.4)	12 (9.5)	1.583 (0.840-2.986)
Lethargy	40 (24.1)	25 (19.8)	1.449 (0.978-2.148)
Stupor	11 (6.6)	5 (4.0)	2.239 (0.832-6.031)
Coma	51 (30.7)	32 (25.4)	1.394 (1.002-1.941)
Metabolic acidosis	6 (3.6)	7 (5.6)	0.651 (0.224-1.888)
Death	1 (0.6)	1 (0.8)	0.759 (0.048-12.019)

NA=not applicable.

confusion, lethargy, stupor, coma, metabolic acidosis, death. For multivariable analysis, the risk for the outcome was described using adjusted odds ratio (AOR) from the binary logistic regression analysis together with 95% confidence interval.

RESULTS

PATIENTS CHARACTERISTICS

In the present study, initially, 880 records of patients with diabetes and hypoglycemia were reviewed, later 401 were met the inclusion criteria, however, after excluding 109 patients, 292 were included for the analysis; 166 in glipizide combined with metformin group and 126 in metformin group (Figure 1). In general, mostly they were female (63.3%) with the median age of 68.5 years old (IQR 58.5-76.6). Their median hemoglobin A1c was 6.7 mg% (IQR 5.9-7.8). Fifty three patients had fever (18.2%), thirty patients were shocks (10.3%), one hundred ninety-three patients had hypertension (66.0%), fourteen

Table 3. Multivariable analysis of risk factors associated with seizure, confusion and lethagy

Factor	Seizure	Confusion	Lethargy
	Adjusted odds ratio (95 % confidence interval)		
Glipizide combined with metformin	1.75 (0.75-4.11)	1.05 (0.36-3.09)	0.90 (0.39-2.10)
Age	0.97 (0.94-1.01)	1.02 (0.97-1.07)	1.00 (0.96-1.04)
Male sex	1.04 (0.44-2.48)	0.88 (0.28-2.79)	0.70 (0.28-1.76)
Hemoglobin A1c	1.11 (0.89-1.39)	0.70 (0.45-1.10)	0.76 (0.55-1.06)
Fever	1.18 (0.36-3.92)	0.76 (0.15-3.91)	1.69 (0.49-5.88)
Shock	2.84 (0.64-12.56)	1.34 (0.17-10.45)	0.14 (0.01-1.46)
Underlying diseases			
Hypertension	1.25 (0.49-3.18)	0.46 (0.14-1.56)	1.30 (0.47-3.59)
Cirrhosis	0.41 (0.04-4.35)	1.57 (0.15-16.24)	0.37 (0.03-4.43)
Chronic kidney disease	1.27 (0.50-3.19)	0.57 (0.15-2.22)	1.81 (0.73-4.48)
Malignant neoplasm	1.21 (0.23-6.33)	5.74 (0.97-34.12)	0.52 (0.05-5.20)

patients had cirrhosis (10.7%), sixty seven patients had chronic kidney disease (22.9%), and fifteen patients had malignancy neoplasm (5.1%). For laboratory variables, their median of serum creatinine was 1.1 mg/dl (IQR 0.8-1.8). Their mean±SD of estimated GFR was 56.4±31.7%.

The glipizide combined with metformin group had higher proportion of patients with shock on the admission (P=0.049) (Table 1). However, median age, proportion of male patients, median hemoglobin A1c, proportion of patients with fever, shock, hypertension, cirrhosis, chronic kidney disease, malignancy neoplasm, median serum creatinine, mean estimated GFR were similar between the two groups.

OUTCOMES

From Table 2, glipizide combined with metformin did not increase the rate of hypoglycemic seizure than that of metformin (24.1% vs. 27.0%; relative risk [RR], 0.89; 95% CI, 0.602 to 1.325). Moreover, there were also no differences between the two study groups in relation to rate of generalized seizure such as tonic-clonic, tonic, clonic, atonic, partial seizure, level of conscious such as confusion, lethargy, stupor, metabolic acidosis and death. For the metformin group, there was no generalized tonic seizure, generalized clonic seizure, generalized atonic seizure. The patients using glipizide combined with metformin had higher rate of coma more than that of metformin group (RR, 1.39; 95% CI, 1.0002-1.941).

FACTORS ASSOCIATED WITH THE OUTCOMES

From the logistic regression analysis glipizide combined with metformin was not associated with increasing the rate of hypoglycemic seizure (AOR, 1.75; 95% CI, 0.75 to 4.11), confusion (11.4% vs. 9.5%; AOR, 1.05; 95% CI, 0.36 to 3.01), lethargy (24.1% vs. 19.8%; AOR, 0.90; 95% CI, 0.39 to

Table 4. Multivariable analysis of risk factors associated with seizure, confusion and lethagy

Factors	Seizure	Confusion	Lethargy
	Adjusted odds ratio (95 % confidence interval)		
Glipizide combined with metformin	1.75 (0.75-4.11)	1.05 (0.36-3.09)	0.90 (0.39-2.10)
Age	0.97 (0.94-1.01)	1.02 (0.97-1.07)	1.00 (0.96-1.04)
Male sex	1.04 (0.44-2.48)	0.88 (0.28-2.79)	0.70 (0.28-1.76)
Hemoglobin A1c	1.11 (0.89-1.39)	0.70 (0.45-1.10)	0.76 (0.55-1.06)
Fever	1.18 (0.36-3.92)	0.76 (0.15-3.91)	1.69 (0.49-5.88)
Shock	2.84 (0.64-12.56)	1.34 (0.17-10.45)	0.14 (0.01-1.46)
Underlying diseases			
Hypertension	1.25 (0.49-3.18)	0.46 (0.14-1.56)	1.30 (0.47-3.59)
Cirrhosis	0.41 (0.04-4.35)	1.57 (0.15-16.24)	0.37 (0.03-4.43)
Chronic kidney disease	1.27 (0.50-3.19)	0.57 (0.15-2.22)	1.81 (0.73-4.48)
Malignant neoplasm	1.21 (0.23-6.33)	5.74 (0.97-34.12)	0.52 (0.05-5.20)

2.10), stupor (6.6% vs. 4.0%; AOR, 3.05; 95% CI, 0.55 to 16.81), coma (30.7% vs. 25.4%; AOR, 1.41; 95% CI, 0.86 to 3.11), metabolic acidosis (3.6% vs. 5.6%; AOR, 0.42; 95% CI, 0.08 to 2.20). (Table 3).

Moreover, age, being male, hemoglobin A1c, having fever, being shock, having hypertension, cirrhosis,chronic kidney disease and malignancy neoplasm were found not to have the association with seizure, confusion, lethargy, stupor, coma and metabolic acidosis.

DISCUSSION

MAJOR FINDINGS

In our study, we found that no differences in relation to rate of hypoglycemic seizure between glipizide combined with metformin and metformin. There were also no different in rate of confusion, lethargy, stupor, coma, metabolic acidosis and death between glipizide combined with metformin and metformin.

STRENGTHS AND LIMITATIONS OF THE STUDY

The present study has several strengths. Firstly, to our knowledge, this is the first study that analyzed hypoglycemic seizure about the association between glipizide combined with metformin and metformin alone. Secondly, this study was presented with many characteristics of the patient. The confounders were indicated and used in the analysis.

However, there were also several limitations of this study. The patients in this study were included in the condition of glipizide combined with metformin and metformin. However, there were other oral hypoglycemic drugs such as pioglitazone, glibenclamide and other combination of oral hypoglycemic drugs were

excluded as well as those with insulin, thus, the findings might not be generalized to a larger group of the population with those medications. Less than half of them (46.2%) had data regarding hemoglobin A1c on the admission or less than three months before admission as any patients were referred from other hospitals and patients had hemoglobin A1c earlier than three months before admission. As we know that hemoglobin A1c was one of confounding factor of hypoglycemic seizure. The precise estimation might not be possible with the high proportion of missing data of this variable. Even though this study showed a similar rate of hypoglycemic seizure in the two groups, still it did not acknowledge dosage of the interested medication which might be one of the factors for hypoglycemic seizure.

COMPARISON WITH PREVIOUS STUDIES

The previous study supports our findings, the patients who age over 65 years had an increased risk of hypoglycemia (rate ratio, 1.36; 95% CI, 1.25 to 1.63).[11] In our study, the median age of patients with hypoglycemia had nearly similar median age in the previous study (68.4 in glipizide combined with metformin group and 68.7 years in metformin group).[11] In the same study, male sex was a protective factor for hypoglycemia (rate ratio, 0.76; 95% CI, 0.65 to 0.90).[11] In our study, the proportion of male patients had less than female (36.7% in glipizide combined with metformin group and 40.1% in the metformin group). In another study, the hypoglycemic patients had mean hemoglobin A1c 7.2 mg%.[21] In our study, hypoglycemic patients had median hemoglobin A1c 6.6 mg% in glipizide combined with metformin and 6.9 mg% in metformin group that the level of hemoglobin A1c was the only difference between the two studies.

CONCLUSION AND IMPLICATION

In conclusion, although there was no difference in relation to the rate of hypoglycemic seizure between the two groups of treatment; using glipizide combined with metformin and metformin alone. For more understanding, a population-based cohort study should be conducted.

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