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Determination of Risk Factors for Mortality in Elderly Patients with Hypoglycemia

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Abstract

The aim of this study was to determine the risk factors for two-terms mortality in elderly patients with hypoglycemic attack in emergency room (ER). A total of 111 (41 males, 70 females) geriatric patients (>65 years) presented with hypoglycemia during a period of between January 2012 to December 2016 were included to the study. The data were obtained by screening the patients' records in our hospital, including age, sex, laboratory parameters, co-morbidities, admission time to hospital, admission results, 15-day and 3-month mortality rates. 63.1% of patients had diabetes mellitus (DM), 51.4% of patients were using OAD and 21.6% were using insulin. The blood glucose levels of the patients who died within the first 15 days after admission were lower than the patients who did not die and it was statistically significant (p=0.014). Blood urea nitrogen (BUN) and creatinin values were significantly higher in patients who died within the first 15 days after admission (p=0.002, p=<0.001). Blood calcium level and platelet (PLT) counts were significantly lower in patients who died within the first 15 days after admission (p=0.006; p=0.001). Red Cell Distribution Width (RDW) was significantly higher in patients who died in the first 15 days after admission (p=<0.001). Neutrophile count was significantly higher in both group patients who died within 15 days and 3 months (p=0.002, p=0.012). Lymphocyte count was significantly lower in patients who died within 3 months (p=0.007). The presence of coexisting DM, coronary artery disease (CAD), hypertension (HT) and malignancy and to use OAD were statistically significant in patients who died within the first 15 days. We found that lower glucose level, impaired renal function, lower calcium and PLT, increased RDW and neutrophile, lower lymphocyte, coexisting DM, CAD, HT, malignancy and to use OAD are risk factors for mortality of geriatric patients with hypoglycemia.

Keywords: Hypoglycemia; Elderly; Emergency; Risk factor; Mortality

Introduction

Hypoglycemia is commonly defined as random blood glucose level less than 70 mg/dL or 3.9 mmol/L however investigators use hypoglycemia thresholds ranging from 3 to 3.9 mmol/L (1,2). Widely known, Whipple triad is used to describe hypoglycemia which including a) low blood glucose level: b) symptoms and signs accompanying low blood glucose level: c) improvement of symptoms with elevated blood glucose level [1]. The incidence of hypoglycemia in the literature differs due to definitions, the age of the population and treatment modalities and also it is difficult to estimate hypoglycemic elderly patients' incidence (older >75 years) [2]. While many hypoglycemia periods are asymptomatic, serious acute complications such as seizure, coma and cardiac arrhythmias may occur [2]. In older people, severe hypoglycemia may lead to serious acute vascular events such as myocardial infarction, acute cardiac decompensation, stroke, ventricular arrhytmias, increased morbidity and mortality [2]. Elderly patients with diabetes mellitus particularly are prone to hypoglycemic periods [3]. Studies have been showed that severe hypoglycemia is a risk factor for lower quality life and cause of mortality [3].

The following study was performed to determine the risk factors for mortality in elderly patients with hypoglycemia in ER. The results from this study will inform to physicians about earlier predicting of geriatric mortality.

Material and Methods

Study design

We conducted a retrospective cross-sectional study based on the patients' records admitted to emergency service in Amasya University Sabuncuoğlu Şerefeddin Research and Training Hospital, Amasya, Turkey. The study protocol was approved by Amasya Provincial Health Directorate and no ethical approval was needed because of retrospective design and as only registry data was used.

We included all patients in the Amasya University Sabuncuoğlu Şerefeddin Research and Training Hospital Emergency Service and with measured hypoglycemia during the dates January 2012 to December 2016. These are the definitions of hypoglycemia according to American Diabetes Association (ADA): Level 1: Blood glucose level is 3.9 mmol/l (70 mg/dl) or less. Level 2: Blood glucose level of <3.0 mmol/l (<54 mg/dl) is adequately low, clinically important hypoglycemia. Level 3: Severe hypoglycemia, indicates serious cognitive impairment demanding support for recovery. Also International Study Group suggests that level of blood glucose <3.0 mmol/l (<54 mg/dl) be defined as clinicaly important hypoglycemia. We studied serious hypoglycemia group of plasma glucose <3.0 mmol/l (<54 mg/dl) according to American Diabetes Association and International Study Group [4].

Age, sex, laboratory parameters, coexisting DM, using OAD and insulin, co-morbidities, admission time to hospital, admission results, 15-day and 3-month mortality data were obtained from the patients' records.

Statistical analysis

Parameters were analysed with SPPS for Windows 23.0 version. The mean of the continuous variables in descriptive statistics was expressed with standard deviation; categorical variables were expressed with

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numbers and percentages. The significance of the difference between the groups was evaluated with Chi-Square Test. Mann-Whitney U Test was used in comparison of binary groups. Kruskal Wallis Test was used in comparison of groups more than two. p<0.005 value was accepted to be statistically significant.

Results

A total of 111 hypoglycemia episodes in elderly patients (>65 years) from 912.500 emergency department cases were recorded during about five-year study period, which was 0.012% of all patients admitted to emergency department. The average age of the patients was 76,2 ± 6,6 and 63.1% (n=70) of patients were female (Tables 1 and 2).

The most common admission hours were 20.00-24.00 (25.2%). HT was the most common concomitant disease among with hypoglycemic geriatric patients. 66% of patients were discharged from ER after the treatment. 15-day mortality was higher than 3-month mortality (Table 3).

The blood glucose levels of the patients who died within the first 15 days after admission were significantly lower than the patients who did not die (p=0.014). BUN and creatinine values were significantly higher in patients who died within the first 15 days after admission (p=0.002, p=<0.001). Blood calcium level and PLTs were significantly lower in patients who died within the first 15 days (p=0.006; p=0.001). RDW was significantly higher in patients who died in the first 15 days (p=<0.001). Neutrophile count was significantly higher in both group patients who died within 15 days and 3 months (p=0.002; p=0.012). Lymphocyte count was significantly lower in patients who died within 3 months (p=0.007) (Table 4).

	mean ± SD / n(%)
Glucose (mg/dL)	37.5 ± 10
BUN	63.5 ± 47.8
Creatinin	1.72 ± 1.33
Na (sodium)	141.5 ± 26.9
K (potassium)	4.56 ± 1.03
Ca (calcium)	8.55 ± 1.17
Hemoglobin (mg/dL)(HGB)	11.9 ± 2.3
Hematocrit (HTC)	36.9 ± 7.6
PLT (10^3)	223.5 ± 100
MPV(mean platelet volume)	8.5 ± 1.7
RDW	16.37 ± 2.88
Neutrophile	7.4 ± 4.6
Lymphocyte	2.2 ± 2

Note: 63.1% (n=70) of patients had DM, 51.4% (n=57) of patients were using OAD and 21.6% (n=24) of patients were using insulin.

Table 1: Complete blood count and biochemical parameters of patients.

	mean ± SD / n(%)
Admission time	
24:00-04:00	15 (13.5%)
04:00-08:00	10 (9%)
08:00-12:00	17 (15.3%)
12:00-16:00	14 (12.6%)
16:00-20:00	27 (24.3%)
20:00-24:00	28 (25.2%)
Co-morbidities	
Asthma	2 (1.8%)
COPD	12 (10.8%)
CAD	41(36.9%)
Renal failure	14 (12.6%)
HT	69 (62.2%)
CAD	18 (16.2%)
Malignancy	7 (6.3%)
Others	10 (9%)
Admission results	
Discharge	66 (59.5%)
Hospitalization in services	20 (18%)
Hospitalization in intensive care unit	22 (19.8%)
Exitus	3 (2.7%)
Mortality	
15-day	21 (18.9%)
3-month	3 (3.3%)

Table 2: Admission time, co-morbidities, admission results and mortality rates of patients.

	3-month mortality			15-day mortality		
	Present	Absent	p	Present	Absent	p
Glucose (mg/dL)	43.3±7.2	38.5±9.5	0.38	32.5±10.9	38.7±9.4	**0.014**
BUN	62.7±21.5	55.2±37.1	0.369	97.9±71.1	55.5±36.6	**0.002**
Creatinin	1.98±1.14	1.41±0.69	0.166	2.99±2.34	1.43±0.7	**<0.001**
Na	137.3±4.2	138.8±5.6	0.513	153.4±60.4	138.8±5.5	0.812
K	4.77±0.78	4.44±0.92	0.411	5.02±1.36	4.45±0.91	0.094
Ca	8±0.79	8.8±0.79	0.054	7.61±1.88	8.77±0.8	**0.006**
HGB (mg/dL)	11.1±0.9	12.1±2	0.317	11.2±3.4	12±2	0.265
HTC	36.8±1.4	37.2±7	0.661	35.4±10.2	37.2±6.9	0.431
PLT	267±27.8	237.3±99.8	0.363	160±81.7	238.3±98.4	**0.001**
MPV	8.5±1.4	8.4±1.7	0.893	9±1.5	8.4±1.7	0.105
RDW	17.9±2.52	15.66±2.07	0.101	19.07±4.05	15.74±2.11	**<0.001**
Neutrophile	14.3±3.6	6.6±4.1	**0.012**	10.1±4.8	6.8±4.3	**0.002**
Lymphocyte	0.8±0	2.2±1.9	**0.007**	2.2±2.6	2.2±1.9	0.052

Table 3: Relationship between mortality and laboratory parameters.

	Mortality in 3 months			Mortality in 15 days		
	Present	Absent	p	Present	Absent	p
Age (years)	72.7±2.1	76.3±6.6	0.29	76.1±6.9	76.2±6.6	0.752
Gender						
Female	2 (66.7%)	57 (65.5%)	0.728	11(52.4%)	59(65.6%)	0.26
Male	1 (33.3%)	30 (34.5%)		10(47.6%)	31(34.4%)	
Admission time						
24:00-04:00	-	13 (14.9%)	0.702	2 (9.5%)	13(14.4%)	0.558
04:00-08:00	-	8 (9.2%)		2 (9.5%)	8 (8.9%)	
08:00-12:00	2 (66.7%)	10 (11.5%)		5 (23.8%)	12(13.3%)	
12:00-16:00	-	11 (12.6%)		3 (14.3%)	11(12.2%)	
16:00-20:00	1 (33.3%)	19 (21.8%)		7 (33.3%)	20(22.2%)	
20:00-24:00	-	26 (29.9%)		2 (9.5%)	26(28.9%)	
Co-morbidities and others						
DM	2 (66.7%)	62 (71.3%)	0.645	6 (28.6%)	64(71.1%)	**<0.001**
OAD	1 (33.3%)	51 (58.6%)	0.383	5 (23.8%)	52(57.8%)	**0.005**
Insulin	1 (33.3%)	21 (24.1%)	0.573	2 (9.5%)	22 (24.4%)	0.237
Co-morbidity	3 (100%)	76 (87.4%)	0.673	18 (85.7%)	79 (87.8%)	0.726
Asthma	-	2 (2.3%)	0.934	-	2 (2.2%)	0.656
COPD	-	10 (11.5%)	0.699	2 (9.5%)	10 (11.1%)	0.596
CAD	2 (66.7%)	36 (41.4%)	0.383	3 (14.3%)	38 (42.2%)	**0.017**
Renal failure	1 (33.3%)	8 (9.2%)	0.274	5 (23.8%)	9 (10%)	0.136
HT	2 (66.7%)	61 (70.1%)	0.662	6 (28.6%)	63 (70%)	**0.001**
CAD	1 (33.3%)	16 (18.4%)	0.471	1 (4.8%)	17 (18.9%)	0.187
Malignancy	-	3 (3.4%)	0.902	4 (19%)	3 (3.3%)	**0.023**
Others	-	7 (8%)	0.782	3 (14.3%)	7 (7.8%)	0.396
Admission result						
Discharge	1 (33.3%)	64 (73.6%)	0.475	1 (4.8%)	65 (72.2%)	**<0.001**
Service	2 (66.7%)	17 (19.5%)		1 (4.8%)	19 (21.1%)	
Critical care	-	3 (3.4%)		19 (90.5%)	3 (3.3%)	
Exitus	-	3 (3.4%)		-	3 (3.3%)	

Table 4: Relationship between mortality and demograhy, admission time, co-morbidities, admission result.

Concomitant DM disease and to use OAD were statistically significant in patients who died within 15 days (p=<0.001; p=0.005). The presence of coexisting CAD, HT and malignancy was significant in those who die within the first 15 days (p=0.017; p=0.001; p=0.023). The relationship between the outcome of the patients and the 15-day mortality was statistically significant (p<0.001).

Discussion

In our study, low glucose, high creatinin and BUN levels were found risk factors for 15-day mortality.

As it is well known, renal disability is an independent risk factor for severe hypoglycemia because metabolization of circulating insulin, reabsorbtion of filtered glucose, a portion of gluconeogenesis, excretion of drugs and metabolization of OAD are some functions of kidneys [5]. Renal impairment causes reduction of the excretion of hypoglycemic agents, the degradation of insulin in peripheral tissues and reduction of the gluconeogenesis [5]. In healthy individuals, the kidney and liver make an equal contribution to gluconeogenesis and glucose releasing into the circulation during the hypoglycemia [5]. In Moen's comprehensive study, chronic renal disease in hypoglycemic patients was a risk factor for 1-day mortality [6]. Age could predict 1-year mortality in hypoglycemic patients but severity of hypoglycemia could

not predict the mortality [7]. Since we received geriatric patients in our study, we investigated risk factors for short-term mortality rather than long-term. In median survival time after discharge was significantly shorter in patients with severe hypoglycemia compared to patients with moderate hypoglycemia [8]. According to our results, short term mortality is higher because severe hypoglycemia and impaired renal function cause more severe acute vascular events in elderly patients.

We found that low calcium level is associated with 15-day mortality of geriatric patients. As known, calcium is an important electrolyte for biological circulations such as membrane potential, hormone secretion, cardiac otomaticity, enzyme activity, extraction-contraction for muscles, synaptic transmission, neuronal conduction and mitosis [9,10]. The impaired parathyroid hormone secretion or action, impaired vitamin D synthesis or action, calcium chelation or precepitation may result in hypocalcemia [11]. Hypocalcemia may causes cardiovascular and neuromuscular insuffiency [11]. Deficiency of calcium concentrations are common in patients have critical illness and reduced plasma calcium level increases the mortality especially in these patients [9,12]. An older patient with comorbidity who presented to ER with hypoglycemia may be considered as a critical patient. Cardio-neurovascular insufficiency caused by hypocalcemia in a critical patient may be a reason of earlier mortality.

It has been demonstrated that high RDW values are associated with increased mortality in general population and particularly patients with cardiovascular disease, acute kidney injury, COPD, hepatitis, congestive heart failure, acute stroke, pulmonary embolism and septic shock [13,14]. RDW is a part of the complete blood count that shows heterogeneity of the red blood cell size [13]. The reason for increased RDW, which has an important role in the differential diagnosis of anemia, is not clear [13,14]. It is known that advanced age and inflammatory process may increase RDW [13,14]. Increased RDW, advanced age, concomitant illness, diabetes and dementia may also predict earlier mortality [14,15]. The high level of RDW in elderly patients is associated with earlier mortality in accordance with the literature.

Reduced PLTs were another risk factor for earlier mortality in elderly patients according to our study. It is shown that PLTs and functions have changes age-related, hematopoietic tissue-related and blood-vascular health [16]. PLTs are stable until middle ages, but they decrease in later ages and effect of aging on PLT functions is not clear [16]. PLTs play an important role in hemostasis and pathological processes of atherosclerosis and arterial thrombosis [17]. The relationship between thrombocytopenia or thrombocytosis and mortality differs in studies. Thrombocytopenia and thrombocytosis were associated with mortality in elderly patients [17] elderly patients, PLTs were not associated with vascular outcomes but low and high PLTs were associated with non-cardiovascular mortality including cancer mortality [18]. Low or high level of PLTs may cause vascular events.

In our study, high neutrophile count was a risk factor for both 15-day and 3-month mortality and low lymphocyte count was a risk factor for 3-month mortality. Briefly, increased neutrophiles and decreasing lymphocytes were important for predicting 3-month mortality. Neutrophiles demonstrate the immediate host response to fungal and bacterial infections, which are commonly responsible for the increased rates of mortality and morbidity, particularly in the older patients [19]. In addition, the number of impaired neutrophiles in diabetic patients may increase the severity of infection [20]. The lower lymphocyte count was a prognostic factor in adults affected by cardiovascular diseases, malignancy and renal insufficieny [21]. Mortality data according to the peripheral blood count parameters differ in the literature.

Nowadays, diabetes is a global health problem and it is the most common reason of mortality due to cardiovascular disease (CVD) [22]. Pharmacotherapy is the main method to administer for diabetic patients by controlling hemoglobin A1c, which is substantial to reduce the risk of cardiovascular events and early mortality [22]. OAD may reduce blood glucose levels while exerting some beneficial effect on CVD risk factors [23]. The potential role of OAD may have on CVD risk is an controversial subject [23]. The blood glucose-lowering effects of OAD and their effects on vasculature and the heart is not clear [23]. OAD associated hypoglycemia was not related to patients with increased mortality risk [24]. In their study, hypoglycemia-associated mortality was not OAD-associated but related to patients with comorbidities [24]. We think that having an additional disease in elderly patients are factors that worsen the current situation.

Conclusion

In conclusion, low glucose level, impaired renal function, low calcium level, high RDW, low platelet count, high neutrophile counts, to use OAD, presence of DM and to have comorbidities such as CAD, HT, malignancy are risk factors for earlier mortality in elderly patients. Nonetheless, these findings must be supported by further studies.

Limitation

The major limitations of the present study are the small sample size of the included patients, lack of the control group, single center experience.

Conflict of Interests

The authors declare no conflict of interests.

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