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Prognostic value of glucose fluctuation in patients undergoing thrombolysis or thrombectomy due to acute ischemic stroke

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Abstract

Background: Hyperglycemia during acute ischemic stroke is associated with worse outcomes, and this glucose altitude may persist in the initial days. In this study, we investigate the effect of glucose fluctuations in the first 4 days in patients diagnosed with acute ischemic stroke and who underwent ivr-tPA ± interventional thrombectomy or only interventional thrombectomy on stroke prognosis. Study was designed bicentered retrospective case series. Patients older than 18 years were included and those suitable for acute treatment, treatment indications, contraindications, and treatment management of hyperglycemia were selected according to the 2018 American Stroke Association guidelines. The effect of fasting glucose values of patients in the first 4 days on admission and 24th hour NIHSS scores, duration of hospitalization, disability, mortality, and prognosis were analyzed. We aimed to demostred the effect of the first 4-day glucose values measured in patients treated in a stroke center on clinical prospect.

Results: One hundred and seventy-six patients were included in the study. Group 1 included 30 (17%) patients with severe clinical condition (NIHSS at admission ≥ 16), and Group 2 comprised 146 (83%) patients with moderate and mild clinical condition (NIHSS at admission < 16). The glucose values of Groups 1 and 2 were found as follows: day 1 (admission): 178.7 ± 10.3 mg/dl and 138.3 ± 54.9 mg/dl, day 2: 197.7 ± 99.8 mg/dl and 137.6 ± 51.8 mg/dl, day 3: 186.1 ± 97.6 mg/dl and 127.5 ± 50.0 mg/dl, and day 4: 169.2 ± 85.0 mg/dl and 126.7 ± 49.3 mg/dl ($p < 0.05$). Mortality risk of patients with glucose ≥ 200 mg/dl was 43.5% on day 1 ($p > 0.05$), 57.1% on day 2, 68.4% on day 3, and 76.5% on day 4 ($p < 0.05$).

Conclusions: The glucose level of patients in severe clinical condition peaked on the second day and that 4 days of resilient severe hyperglycemia is a negative risk factor for sequela and mortality.

Keywords: Acute ischemic stroke, Glucose, Thrombolysis, Thrombectomy

Background

Approximately 80–85% of cerebrovascular diseases (CVD) occur as ischemic stroke [1]. In the acute period, 40–50% of the patients who had a stroke are detected with hyperglycemia, which, in the early stages, increases the size of the infarction, worsens clinical outcomes, and increases mortality [2]. According to a study, hyperglycemia was detected in patients with non-lacunar stroke. It was found that hemorrhagic transformation and poor prognosis were higher in this group, in other words, undesirable complications were seen more frequently in this group [3]. Transient hyperglycemia was detected in 5–40% of the patients who were not diagnosed with diabetes mellitus but presented to the hospital due to ischemic stroke. This may be due to multifactorial and previously undetectable DM, impaired glucose tolerance and insufficient exercise capacity due to loss of strength caused by ischemic stroke, and insufficiency of the pituitary–sympatho-adrenal axis or its reaction to

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stress [4]. Consequently, hyperglycemia occurring in the acute period extends the duration of hospital stay, thus increasing cost and mortality [5]. During predictive risk assessment in patients administered with intravenous recombinant tissue plasminogen activator (iv r-tPA), the presence or absence of hyperglycemia, severity of stroke, and time of initiation of treatment are highly important in terms of prognosis and mortality [6]. We believe that hyperglycemia may provide predictive results on the clinical course for the patient group undergoing this treatment. Based on this hypothesis, we demonstrate the effect of glucose fluctuations on the clinical prognosis of patients diagnosed with acute ischemic CVD in our stroke centers and treated with ivr-tPA ± thrombectomy or only interventional thrombectomy in the first 4 days.

Methods

One hundred and seventy-six patients with acute ischemic CVD and who underwent iv r-tPA and/or thrombectomy between November 1, 2018, and May 1, 2020, were included in the study. Patients older than 18 years were included and those suitable for acute treatment, treatment indications, contraindications, and treatment management of hyperglycemia were selected according to the 2018 American Stroke Association (ASA) guidelines [7]. Patients, presenting within the first 4 h of stroke symptoms, without hemorrhage in brain CT or hypodensity in the infarct area were evaluated according to the ASA guidelines. Patients with endocrine disorders (cushing syndrome, insulinoma…) and those with diseases or using drugs that could disrupt glucose metabolism, such as corticosteroids, were excluded from the study. At the same time, patients who developed hemorrhagic transformation after the treatment procedure or had a decompressive surgery were also excluded in the study. The number of patients was determined according to G-power analysis [(glucose levels (mg/dl), group 1; 178 ± 43—group 2; 155 ± 34), effect size:0.59, α:0.05, β-1:0.80]. According to this result, it was determined that there should be a minimum of 72 patients. The age, gender, treatment method, duration of treatment, NIHSS score, fasting blood sugar level in the first 4 days, HbA1c level and mRS score, and discharge status of patients were analyzed.

Patients were divided into two clinical severity groups based on the NIHSS score at admission. Patients with a severe clinical presentation were included in the first group (NIHSS ≥ 16) and those with a moderate/mild clinical presentation were included in the second group (NIHSS < 16). The mRS score was used to assess sequelae and dependency. In this study, the glucose level of < 140 mg/dl was evaluated as normoglycemia, ≥ 140 mg/dl as hyperglycemia, and ≥ 200 mg/dl as severe hyperglycemia. This classification has been used in some studies for stress hyperglycemia [8]. Blood sugar levels at admission were used as the data for the first day. On other days, fasting blood sugar levels were measured between 6.00 am and 8.00 am in the morning.

Data were obtained from the hospital database and patient files and scanned and evaluated by two researchers separately. The serum glucose levels were measured from venous blood by the photometric method using Abbott® Laboratories, Architect® c1600. HbA1c was studied on Arkray® and Mindray® BC 6800 devices in EDTA hemogram tubes.

CVD was diagnosed using cranial computed tomography and/or cranial magnetic resonance. Patients who arrived four and a half hours from the symptom to needle time were treated. IV alteplase vial (Actilyse®) 0.9 mg/kg, (max. 90 mg) was used for thrombolysis, with 10% of total dose used as bolus and the remaining used as 45–60 min infusion.

Siemens® digital subtraction angiography device was used in the angio unit. In patients receiving interventional treatment, entry was made from the right femoral artery with a 7f sheath, and a 5f hydrophilic diagnostic catheter (Cordis®) and 0.035 hydrophilic guide wire (Aquatrack®) were used to diagnose the lesion. A 6f guiding catheter (Destination®) was inserted into the internal carotid artery proximal for endovascular intervention. A 5f distal access catheter 0.014 microcro wire (Syncro®) was inserted into the ICA cavernous segment, and thrombus distal was passed with a microcatheter (Rebar® 27). A stent retriever (Solitare Platinum® 6/40) was placed on the lesion through the microcatheter, and retrieval and aspiration were performed. During the procedure, 200 ml of contrast agent and 5,000 iu IV heparin were used. During the procedure, patients were sedatized by an anesthesiologist.

Study data were analyzed using the SPSS for Windows, Version 20.0 (2012) package program. Bivariate correlation (Pearson's R and Spearman tests) was used to assess the correlation between the data. The chi-square test was conducted for categorical data, and the mean, standard deviation, number, and percentage values were calculated. Groups were initially analyzed for their suitability to normal distribution. Shapiro–Wilk and skewness—kurtosis values were used in the analysis. The variance analysis was used for repeated measurements and the Mann–Whitney U test for the analysis of independent variables without normal distribution; $p < 0.05$ was considered statistically significant in all analyses.

Results

This study was conducted in two stroke centers and 176 patients (95 women and 81 men) with a mean age of 70.07 ± 13.07 years were included. Of the patients, 58.5% underwent iv r-tPA, 10.2% underwent interventional thrombectomy, and 31.3% underwent iv r-tPA + interventional thrombectomy. Symptom-to-needle time was measured as 171.4 ± 51.9 min, and mortality rate was 27.3% (Table 1).

Admission and 24th hour NIHSS scores were 11.4 ± 4.2 and 9.5 ± 5.3, respectively. Group 1 included patients in severe clinical condition (NIHSS ≥ 16) and Group 2 comprised those in moderate to mild clinical condition (NIHSS < 16). NIHSS at admission was ≥ 16 in 17% of the patients and < 16 in 83% of the patients. Admission and 24th hour NIHSS scores were 17.3 ± 2.1 and 18.2 ± 2.2 in Group 1 and 9.8 ± 3.4 and 7.7 ± 3.7 in Group 2 ($p < 0.05$). We examined in detail the relationship of HbA1c and DM history with clinical severity (Table 2).

To demonstrate the glucose fluctuation that constituted the main focus of our study, the glucose value measured at admission was accepted as day 1 value and the consecutive measurements up to day 4 were analyzed. Based on the NIHSS score at admission, the glucose values and statistical analysis of Groups 1 and 2 were as follows: day 1: 178.7 ± 10.3 mg/dl and 138.3 ± 54.9 mg/dl, day 2: 197.7 ± 99.8 mg/dl and 137.6 ± 51.8 mg/dl, day 3: 186.1 ± 97.6 mg/dl and 127.5 ± 50.0 mg/dl, and day 4: 169.2 ± 85.0 mg/dl and 126.7 ± 49.3 mg/dl (p < 0.05) (Fig. 1). HbA1c values based on NIHSS scores at admission were 7.39% ± 1.53% in Group 1 and 6.29% ± 1.31% in Group 2 ($p < 0.05$). Of the patients, 41.5% (*n*:73) had a known DM diagnosis. In addition, 70% (*n*:21) of the patients in Group 1 and 35.5% (n:52) of the patients in Group 2 had diabetes ($p < 0.05$) (Table 3).

When glucose values were analyzed according to 24th hour NIHSS scores, we notice that the patients in Group 1 had significantly higher glucose levels in all four measurements (Table 2).

To examine the effect of glucose fluctuation on mortality, we analyzed the glucose values of surviving and deceased patients as follows: day 1: 136.4 ± 51.4 mg/dl and 169.4 ± 95.8 mg/dl, day 2: 131.2 ± 44.1 mg/dl and 194.7 ± 91.8 mg/dl, day 3: 121.7 ± 40.5 mg/dl and 181.8 ± 91.9 mg/dl, and day 4: 119.9 ± 37.8 mg/dl and 173 ± 84.6 mg/dl (p < 0.05). The mortality rate was 42.5% for those diagnosed with DM and 16.5% for those not diagnosed with DM (p < 0.05). The mortality risk of patients with glucose of ≥ 200 mg/dl was 43.5% on day

Table 1 General clinical information

Age	70.07 ± 13.07
Gender (f–m)	95 (54%)–81 (46%)
Symptom-to-needle/min	171.4 ± 51.9
Iv-r tPA, *n*	103 (58.5%)
Mechanical thrombectomy, *n*	18 (10.2%)
Iv-r tPA + mechanical thrombectomy, *n*	55 (31.3%)
Expired, *n*	48 (27.3%)

f female, *m* male

Iv r-tPA Intravenous recombinant tissue plasminogen activator

Table 2 Relationship of clinical severity with DM and HbA1c

Clinical Parameters	Variables	*p*
Baseline NIHSS *mean-n*	11.4 ± 4.2–176	0.000
Baseline NIHSS ≥ 16	17.3 ± 2.1–30 (17%)	
< 16	9.8 ± 3.4–146 (83%)	
24th hour NIHSS *mean-n*	9.5 ± 5.3–176	0.000
24th hour NIHSS ≥ 16	18.2 ± 2.2–29 (16.5%)	
< 16	7.7 ± 3.7–147 (83.5%)	
DM history *yes/total, n*	73/176 (41.5%)	0.001
Baseline NIHSS ≥ 16	21/73 (28.8%)	
< 16	52/73 (71.2%)	
DM history *no/total, n*	103/176 (58.5%)	0.001
Baseline NIHSS ≥ 16	9/103 (8.7%)	
< 16	94/103 (91.3%)	
HbA1c ≥ 6.5% / total, *n*	80/176 (45.5%)	0.001
Baseline NIHSS ≥ 16	22/80 (27.5%)	
< 16	58/80 (72.5%)	
HbA1c % mean (total)	6.48 ± 1.41	0.000
Baseline NIHSS ≥ 16	7.39 ± 1.53	
< 16	6.29 ± 1.31	

DM Diabetes Mellitus

NIHSS National Institute of Health Stroke Scale

HbA1c Hemoglobin A1c

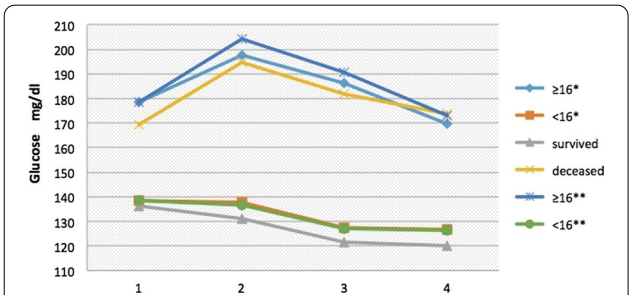

Fig. 1 Effect of glucose levels in the first 4 days on clinical severity and mortality. *baseline NIHSS **24th hour NIHSS

Table 3 Relationship of glucose level in the first 4 days with clinical score and prognostic factors

	Day 1	*p*	Day 2	*p*	Day 3	*p*	Day 4	*p*
Glucose levels (mg/dl)								
NIHSS ≥ 16*	178.7 ± 10.3	0.003	197.7 ± 99.8	0.000	186.1 ± 97.6	0.000	169.2 ± 85.0	0.000
NIHSS < 16*	138.3 ± 54.9		137.6 ± 51.8		127.5 ± 50.0		126.7 ± 49.3	
NIHSS ≥ 16**	178.4 ± 107.8	0.004	204.2 ± 100.5	0.000	190.7 ± 98.1	0.000	173.1 ± 86.5	0.000
NIHSS < 16**	138.6 ± 54.6		136.7 ± 50.6		127.0 ± 49.4		126.2 ± 48.6	
Expired	169.4 ± 95.8	0.004	194.7 ± 91.8	0.000	181.8 ± 91.9	0.000	173.0 ± 84.6	0.000
Survived	136.4 ± 51.4		131.2 ± 44.1		121.7 ± 40.5		119.9 ± 37.8	
Mortality risk ratio								
glc ≥ 200 mg/dl	43.5%	0.056	57.1%	0.000	68.4%	0.000	76.5%	0.000
glc < 200 mg/dl	24.8%		20.7%		21.5%		21.5%	
mRS—30th day								
glc ≥ 200 mg/dl	4.19 ± 1.2	0.003	4.40 ± 1.05	0.001	4.44 ± 1.33	0.007	4.75 ± 1.48	0.001
glc < 200 mg/dl	3.24 ± 1.1		3.26 ± 1.17		3.32 ± 1.17		3.29 ± 1.15	

*baseline NIHSS **24th hour NIHSS

NIHSS National Institute of Health Stroke Scale

glc Glucose

mRS modified Rankin Scale

1 ($p > 0.05$), 57.1% on day 2, 68.4% on day 3, and 76.5% on day 4 ($p < 0.05$) (Table 2).

To assess the improvement and sequelae status of patients, we analyzed the mRS, which was measured in the first month of the disease. We also examined the effect on sequelae by comparing the high glucose group (≥ 200 mg/dl) and low glucose group (< 200 mg/dl). The mRS averages of the group with daily glucose of ≥ 200 mg/dl were 4.19 ± 1.2 on day 1, 4.40 ± 1.05 on day 2, 4.44 ± 1.33 on day 3, and 4.75 ± 1.48 on day 4. The sequelae rate was significantly higher compared with that of the other group ($p < 0.05$).

Discussion

Acute ischemic stroke is as critical and satisfactory results can be obtained when iv r-tPA ± thrombectomy is applied at an early stage, namely, clinical recovery increases sequelae rate and mortality decrease. The major parameters that can serve as predictory criteria for clinical prognosis include size of the infarct, duration of the intervention, and location of the occluded artery. However, we believe that the glucose values of patients during this period could also give a preliminary idea of the clinical process. We found that the glucose fluctuation noted in the early days of the disease was significantly associated with parameters, such as clinical severity, degree of sequelae, and mortality rate. To reveal the effects of this connection on the above parameters more clearly and meaningfully, we formed a group that included only patients who underwent acute treatment (iv r-tPA ± thrombectomy). Time to treatment from disease onset was 171.4 ± 51.9 min, which is optimal for treatment. In similar studies in literature, a single glucose value was usually analyzed along with all treatment options. Therefore, we wanted to draw attention to the fluctuation of glucose in the first several days, including groups of acute intervention.

Hyperglycemia is an extremely important factor in the development of atherosclerosis and associated vascular complications [9]. The importance of various metabolic abnormalities and subsequent formation of reactive oxygen radicals in pathophysiology are discussed in detail below.

Acute hyperglycemia initially disrupts nitric oxide synthesis, causing disturbances in the production of prothrombotic and vasoactive substances [9]. Vasoconstriction leads to microcirculation and increases ischemia, as post-thrombosis recanalization cannot be achieved [10]. Increased lactate production in brain due to hyperglycemia is considered to be associated with a decrease in penumbra in stroke patients [11]. In addition, hyperglycemia and hyperinsulinemia, which occur in acute ischemic stroke, can reduce fibrinolytic activity and increase the ratio of plasminogen activators–inhibitors, thus reducing the effect of iv r-tPA and recanalization [12]. Based on these two outcomes, we can say that hyperglycemia causes a vicious cycle in stroke patients as a cause and result of treatment success. In other words, we can assume that if this cycle is broken, clinical recovery will accelerate. We noted this in our study, for instance we found higher mortality rates in patients with glucose of ≥ 200 mg/dl for 4 days. Patients were evaluated

1 month after the post-stroke for clinical improvement. When we examine the relationship of baseline glucose values to mRS scores on the 30th day, while the mRS was 4.19 ± 1.2 in patients with glucose ≥ 200 mg/dl, it was 3.24 ± 1.1 in patients with < 200 mg/dl. As a result, when we consider the 30th day mRS scores of patients with glucose < 200 mg/dl, we found that these patients showed a higher rate of clinical improvement.

A study on ischemic stroke conducted with experimental animal models shows that monocyte/macrophages, which are neuroprotective, non-inflammatory cells involved in neurogeneration, are decreased in ischemic brain, where hyperglycemia occurs. The study also indicates that glucose metabolites, such as alpha-dicarbonyl, one of the final products of glycolization in ischemic brain tissue, increases in hyperglycemic mice [13]. Another experimental study emphasizes that hyperglycemia causes brain edema by increasing the permeability of the blood brain barrier and release of inflammatory mediators [14]. Some studies also suggest that hyperglycemia aggravates the clinical prognosis by causing an increase in the size of the existing infarction. In a study conducted with experimental animals, the MCAs of the animals were subjected to occlusion by suturing. Blood glucose levels were brought to 140–200 mg/dl (mild hyperglycemia) and 240–350 mg/dl (severe hyperglycemia) with 30 and 60% glucose solutions, respectively. There was no significant difference between the mild hyperglycemic group and the control group in terms of infarction size, while a significant increase in infarction size was found in animals with severe hyperglycemia ($p = 0.029$) [15].

We evaluated the relationship between clinical severity and glucose levels over 4 days, which is the focus of our study, based on the NIHSS score at admission. Accordingly, we showed that glucose levels were higher in the severe patient group (NIHSS < 16) compared with the mild to moderate patient group (NIHSS < 16). This result was valid for all 4 days when glucose levels were recorded and yielded a significant statistical result in favor of poor prognosis.

In terms of mortality, the course of glucose was similar in the group of severe patients. Therefore, the analysis of glucose follow-up reveals that glucose elevation is directly related to and increases the mortality risk. Another interesting result was that glucose peaked on day 2 in deceased patients and the severe group of patients with baseline and 24th hour NIHSS ≥ 16. We did not encounter a similar peak on day 2 in mild to moderate and surviving patients. Based on this result, we can assume that the clinical prognosis is more likely to deteriorate, especially in patients whose blood sugar cannot be controlled in the first 24 h. However, the prognosis should not be concluded based on the glucose level on day 1; waiting for days 2 and 3 and checking for a peak can provide better prediction.

In a comprehensive literature study on this topic, hyperglycemia, as one of the causal factors of the negative consequences of stroke, was identified as a changeable risk factor, and it was concluded that the risk of mortality decreases in case of blood sugar regulation [16]. According to a meta-analysis study, each 1 mmol/L increase in blood sugar increases the negative clinical course by 8% and the rate of intracranial hemorrhage by 9% [17]. Acute hyperglycemia detected in acute stroke patients leads to in-hospital mortality and insufficient post-discharge functional recovery in non-diabetic patients. It is also suggested that hyperglycemia is not always associated with DM but can also be considered a stress response to hypercortisolism [16]. In this study, individuals with no DM history had a high risk of severe disease progression, which supports the conclusion in the previous sentence. In addition to transient hyperglycemia, HbA1c is also significantly higher in severe patients compared with mild to moderate ones. This may also suggest that severe patients are prone to diabetes or are in the prediabetic stage.

In a study conducted between 2000 and 2003, the effect of glucose level on recanalization time and clinical outcomes were investigated in acute stroke patients receiving iv thrombolysis. In addition, the intra-arterial obstruction rate was monitored with a transcranial doppler ultrasonography. The NIHSS of the hyperglycemic group was 17.0 ± 5.5% and the occlusion rate was 52.2%, while the NIHSS of the normoglycemic group was 15.8 ± 5.5% and the occlusion rate was 31.4% ($p = 0.05$). The recanalization success rate of hyperglycemic and normoglycemic patients was 24.6 and 39%, respectively, which was significantly lower in the hyperglycemic group ($p = 0.001$). When the average recanalization time was compared between hyperglycemia and normoglycemia, it was found to be longer in hyperglycemic patients. In addition, recanalization times were 163 ± 79 min and 131 ± 90 min in severe hyperglycemia and less severe hyperglycemia (glucose:140–200 mg/dl), respectively ($p = 0.045$). Based on these data, it was reported that if hyperglycemia is present in acute stroke patients, the success rate of recanalization after iv r-tPA is lower [8].

One hundred and three acute stroke patients with mean age of 55.5 ± 15.3 years were included in a prospective study conducted in Ethiopia in 2016. The first glucose value measured was ≥ 140 mg/dl in 49.5% of the patients. The glucose value of normoglycemic patients was 119.9 ± 13.0 mg/dl and that of hyperglycemic patients was 183.2 ± 34.5 mg/dl. Mean NIHSS was 14 in hyperglycemic patients and 11 in normoglycemic patients,

while the risk of poor prognosis was 3.83 times higher in hyperglycemic patients ($p=0.041$) [18]. As a result these two studies also supports our hypothesis.

In this study, we observed a steady daily increase in the 30-day mRS score in patients with severe hyperglycemia (day 1: 4.19 ± 1.2, day 2: 4.40 ± 1.05, day 3: 4.44 ± 1.33, day 4: 4.75 ± 1.48). However, no such increase was observed in patients who did not have severe hyperglycemia. In other words, we noted an increase in the risk of disability for every passing day that glucose control was not achieved. Regarding the relationship between these two groups, in 4 days, the sequelae ratio, such as the mRS score, is higher in severe hyperglycemic patients ($p<0.05$). In general, based on these results, we can argue that resistant hyperglycemia in the early days negatively impacts sequelae and dependency.

In a study that supports our hypothesis, there was a significant relationship between hyperglycemia and short-term recovery and impaired functionality in patients with acute stroke; furthermore, achieving normoglycemia in the early stage of stroke positively impacted the quality of life and prognosis of patients [8]. In a similar study, hyperglycemic and normoglycemic patients were followed up for 3 months and it was found that the clinical functional capacity was lower in hyperglycemic patients ($p=0.011$). As a result, it was emphasized that the post-stroke sequelae would be more severe and longer [17]. According to European Cooperative Acute Stroke Study II results, hemorrhagic transformation, adverse clinical outcomes, and increase in mortality were reported in case of 24 h or longer hyperglycemia. Furthermore, based on NIHSS and mRS scores in hyperglycemic patients, it was also emphasized that clinical improvement was worse in these patients [19]. We exclude patients who developed hemorrhagic transformation in our study. Because, some of these patients underwent decompressive surgery. We thought that stress due to decompressive surgery or hemorrhagic transformation in non-surgical patients might affect the 4-day glucose values. In addition, due to the small number of patients with hemorrhagic transformation, it was thought that it would be an insufficient population for statistical assessment. However, this issue could be discussed in a future meta-analysis with more participants.

Conclusions

In this study, we argue that the course of glucose in the early stage can give a preliminary idea of the clinical course in acute ischemic stroke patients. Limited studies include acute intervention groups (r-tPA ± interventional) and draw attention to the fluctuation of glucose in the initial days. We believe that the glucose peak on day 2, particularly in severe patients, can be a negative predictor of mortality and sequelae. The predictive value of glucose fluctuation in stroke patients can be investigated with more comprehensive studies.

Abbreviations

CVD: Cerebrovascular Diseases; DM: Diabetes Mellitus; ASA: American Stroke Association; Iv r-tPA: Intravenous recombinant tissue plasminogen activator; mRS: Modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; ICA: Internal Carotis Artery.

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Not applicable.

Authors' contributions

SC, AA, and YA conceived of the study, and participated in its design and coordination and helped to draft the manuscript. AA and UO participated in the design of the study and performed the statistical analysis. All authors have agreed to conditions noted on the Authorship Agreement Form. All authors read and approved the final manuscript.

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Availability of data and materials

The complete de-identified dataset is available from the corresponding author on a reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Malatya Clinical Research (approval number: 2020/118) and the principles of the Helsinki Declaration were followed. Written informed consent was obtained from the patients participating in the study, or their first degree relatives if the patient was unable to provide consent, after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

Consent for publication

Not applicable.

Competing interests

All authors declare that they do not have any competing.

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