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ORIGINAL ARTICLE **ARAŞTIRMA YAZISI**

BLOOD GLUCOSE VARIABILITY DURING THE FIRST 24 HOURS AND PROGNOSIS IN ACUTE STROKE PATIENTS TREATED WITH IV THROMBOLYSIS

Mehmet Yasir PEKTEZEL, Ezgi YILMAZ, Ethem Murat ARSAVA, Mehmet Akif TOPÇUOĞLU

Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, TURKEY

ABSTRACT

INTRODUCTION: Hyperglycemia in acute ischemic stroke decreases the effectiveness of intravenous tissue plasminogen activator (IV tPA) and increases its hemorrhagic complications. Therefore, optimization of blood glucose (BG) is suggested. But, no consensus is achieved on which of the BG parameters to be used such as admission BG, post-treatment BG, first day maximum and average BG (maxBG and aveBG), or BG variability indices such as the standard deviation of mean BG (SDBG), coefficient of variation of BG (CVBG) and J-index.
METHODS: Admission and 24h BG were measured in 145 acute stroke patients (55% female, age: 70±13 yr; NIHSS: 14 ± 6, symptom-to-needle time: 160 ± 58 minutes) treated with IV tPA. BG variability indices were evaluated in 107 patients with serial BG measurement available.
RESULTS: AveBG was significantly higher in patients with 3rd month mRS>2 (46.2%), but admission BG, SDBG, CVBG and J-index were not significantly different. An exploratory regression analysis indicated that the connection of aveBG to worse prognosis (β=-0.155, p=0.045) persisted after adjustment for admission NIHSS, age and DM history. No BG parameter predicted symptomatic tPA-associated type-II intracerebral hemorrhage (6.7%), albeit these patients had marginally higher average BG levels (p=0.045). Presence of diabetes, HbA1c, admission BG, average first day BG and variability indices had not modified the beneficial (52%) and dramatic response (28%) to IV tPA.
DISCUSSION and CONCLUSION: Sustained hyperglycemia, not glucose variability, during the first 24 hour predicts poor prognosis in acute stroke patients treated with IV thrombolysis.
Keywords: Stroke, glucose, sugar, glycemia, tPA, thrombolysis, thrombolytic, efficacy.

AKUT İSKEMİK İNMEDE İLK GÜN İÇİNDEKİ KAN ŞEKERİ DEĞIŞKENLİĞİ VE İNTRAVENÖZ DOKU PLAZMİNOJEN AKTİVATÖRÜNE YANIT

ÖZET

GİRİŞ ve AMAÇ: Akut iskemik inmede hiperglisemi, intravenöz doku plazminojen aktivatörünün (IV tPA) etkinliğini azaltıp, hemorajik komplikasyonlarını arttırabilir. Bu nedenle, IV tPA uygulanan olgularda kan şekeri (KŞ) optimizasyonu temel öneriler arasındadır. Ancak, bu amaçla KŞ ve değişkenliğini gösteren giriş KŞ, tedavi sonrası KŞ, ilk gün maksimum ve ortalama KŞ (maksKŞ ve ortKŞ), ortalama KŞ standart sapması (KŞSD), KŞ varyasyon katsayısı (KŞCV) ve J-endeksi gibi parametrelerin hangisinin kullanımının en uygun olduğu açısından görüş birliği yoktur.
YÖNTEM ve GEREÇLER: IV tPA ile tedavi edilen 145 akut inme hastasında (% 55 kadın, yaş: 70 ± 13 yıl; NIHSS: 14 ± 6, semptom-iğne zamanı: 160 ± 58 dakika) tedavi öncesi ve 24. saat KŞ ölçüldü. KŞ değişkenlik göstergeleri ise seri KŞ ölçümü yapılabilen 107 olguda incelendi.
BULGULAR: Üçüncü ay modifiye Rankin skoru (mRS) > 2 olanlarda (%46,2) IV tPA uygulamasının ilk günü ortalama KŞ anlamlı olarak yüksek iken, giriş KŞ, KŞSD, KŞCV ve J-endeksinde farklılık gözlenmedi. Regresyon analizi modellemesi ortalama KŞ yüksekliği ile kötü prognoz bağlantısının kabul NIHSS, yaş ve DM öyküsü ile uyarlandıktan sonra da devam ettiğini göstermiştir (β=-0,155, p=0,045). OrtKŞ, tPA ilişkili tip-II intraserebral kanama hastalarında (%6,7) daha yüksek olsa da (p=0,045), KŞ parametreleri bu modellerde genel olarak semptomatik kanama riskinin öngörülebilmesi

Corresponding author: Mehmet Akif Topcuoglu, Prof. MD. Hacettepe University, Faculty of Medicine, Department of Neurology, 06100 Sıhhiye, Ankara, Turkey.
Telephone: +90 312 305 18 06 **E-mail:** matopcuoglu@yahoo.com
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kapsamında bağımsız gösterge belirmemiştir. Diyabet varlığı, HbA1c, giriş KŞ, ortKŞ ve KŞ değişkenlik indisleri IV tPA'dan yararlanma (% 52) ve dramatik yanıt verme (% 28) olasılığını anlamlı olarak etkilememiştir.
TARTIŞMA ve SONUÇ: : IV tromboliz ile tedavi edilen akut inmeli hastalarda kötü prognozun öngörülmesi bağlamında 24 saat boyunca sürekli hiperglisemi olması du dönemdeki kan şekeri değişkenliğinden daha önemli bir belirteçtir.
Anahtar Sözcükler: İnme, glukoz, şeker, glisemi, tPA, tromboliz, trombolitik, yarar.

INTRODUCTION

Diabetes is a significant interchangeable risk factor for all cardiovascular diseases, including stroke. [1, 2] In addition, the high blood glucose level (usually defined as ⍰140 mg/dL) following an acute ischemic vascular event is a significant factor that worsens the prognosis always [3, 4]. Hyperglycemia increases the rate of complications after acute ischemic stroke, while adversely affecting the fate of ischemic tissue [5, 6]. In cases with acute ischemic stroke treated with intravenous (IV) recombinant tissue plasminogen activator (tPA), it was observed that high blood glucose levels before treatment and its remaining high after treatment decreased tPA response rate, i.e recanalization/reperfusion rate, in most of the studies and increased the risk of tPA complication, ie reperfusion bleeding [7-11]. In cases with high blood glucose levels, there is a high risk of inadequate clinical outcome and significant deficit (modified Rankinscale-mRS>2) in the third month with IV tPA, the mortality and post-treatment symptomatic intracerebral hemorrhage (sICH) [4, 9-12]. These adverse effects are more significant as long as the start of medication with IV tPA delays and the blood glucose level reaches up to a certain level [4, 13].

On the other hand, it is not exactly known whether the blood glucose variability (Glycemic variability, GV) becomes more prominent in acute conditions, which is associated with the development of vascular complications in diabetes and is generally increased with the progression of the disease [14]. Glycemic variability expansion was shown to increase in-hospital mortality in critical medical diseases, especially in sepsis, and to increase both mortality and major cardiac complication rates in acute coronary syndromes [15-19].

Similarly, some studies showed the relation of increased blood glucose variability in early period in patients with diabetic acute stroke with early neurological worsening and increased risk of cardiovascular mortality with functional poor prognosis for the third month. [20-22] However, this relation was not set forth in all studies [23].

The effect of blood glucose variability on prognosis in diabetic and non-diabetic stroke patients who were administered with IV tPA in acute period was also discussed in various series, however, quite different results were published [14, 23]. The aim of this study is to review these results and to determine the effect of blood glucose level and its variability on thrombolytic response in a more homogenous acute stroke group who were treated with IV tPA.

MATERIAL AND METHODS

Patients: 145 consecutive patients with acute ischemic stroke who received intravenous tPA treatment for the past 9 years and whose blood glucose levels could be achieved on the first day were included in this retrospective analysis. The clinical and imaging data were extracted from our prospectively collected corporate stroke database; transthoracic echocardiography, 24-hour Holter, diffusion-weighted magnetic resonance imaging, and at least one craniocervical angiography, all constitute the minimum level of protocol that this prospective database was based upon.

The national standard IV tPA administration protocol and metrics were complied with to the maximum extent in all patients. The study protocol and the database were approved by the local ethics committee. Patients with acute stroke who were treated by interventional techniques such as thrombectomy were excluded from the study.

The clinical stroke weight was assessed before IV tPA, 24 hours after IV tPA and at discharge by National Institutes of Health Stroke Scale (NIHSS) [24]. Functional outcome at the end of third month was assessed by modified Rankin score (mRS) as the main criterion for stroke prognosis [25]. "Favorable response" to IV tPA was defined as reduction of NIHSS more than 4 points after administration or its drop to 0 or 1 point at the end of 24 hours following IV tPA. When the reduction of NIHSS is 8 points or greater, it was classified as "dramatically favorable response" to IV tPA [26]. The prognosis was defined as "good" when mRS is 2 or lesser (0,1,2), and as "excellent"

when it is 0 or 1. The Causative Classification of Stroke algorithm was used for "Stroke Etiologic Classification" [27].

Blood glucose variables: Electronic and written files were reviewed in a way to reflect the retrospective nature of the study, and both finger-tip blood and bedtime blood glucose values were noted. Blood glucose level above 140 mg/dL was considered as hyperglycemia. Hemoglobin A1c>7% in the hyperglycemic patients with no previous diabetes diagnosis was considered as new-diagnosis diabetes. The glucose level was checked 2,6±1,6 times in patients with positive diabetes history, and 2,1±1 times in patients with no positive diabetes history.

The blood glucose levels studied: The blood glucose first measured in the emergency department (pre-treatment BG); blood glucose at the 24th hour (24th hour BG); First day average blood glucose (24-hour average BG); Standard deviation of average blood sugar on the first day (24-hour BG SD), 24 hour blood glucose variation coefficient (Formula: "SD/average"; 24-hour BG CV) and J index (Formula: (average blood glucose +SD) 2", mg/dL, J-index) [28]

Statistics: All values were given as "average + standard deviation [SD]", 95% confidence interval [95% CI] "percentage" or "median", according to the situation. The distribution normality was assessed by Kolmogorov-Simirnov and Shapiro-Wilks tests. Mann-Whitney U/ Student-t, "paired-t" and Chi-square / "exact" tests were used where necessary to determine the differences between the groups. Multivariate models were established to determine the effect of blood glucose parameters on tPA, tPA-related "symptomatic intra-parenchymal hemorrhage", efficacy of IV tPA and its effect on 3-month positive outcomes. The variables that provided "0,1"p value in the first stage of the models were accepted to the final analysis. The level of statistical significance was set at $p < 0.05$. SPSS version 22 was used for all calculations.

RESULTS

It was found that 52% of 145 cases included in the study (55% women, age: 70 ± 13 years, NIHSS: 14 ± 6; onset-to-tPA administration interval: 160 ± 58 minutes) responded positively and 28% thereof responded dramatically to IV tPA. No significant difference was found in the blood glucose at the time of arrival and average blood glucose as well as glucose variability parameters for these patients who positively responded to tPA and for whom a better prognosis, less hospitalization duration and less hemorrhagic complication were observed. However, HbA1c and average blood glucose in the first 24 hours were numerically high in the patients with poor IV tPA response (Table I).

At the end of third month, the rate of good clinical outcome (mRS 0-2) was found as 46,2% and excellent outcome (mRS 0-1) was 33%. The duration of hospitalization, symptomatic intracerebral hemorrhage and main artery occlusion were lower in these patients, as expected. Age, pre-treatment NIHSS and hypertension adversely affect, that's decrease, the positive functional outcome in both categories. On the first day, the average blood glucose was significantly higher in patients who did not have a good functional outcome (21 mg/dL more averagely, $p=0.008$ for mRS 0-1; $p=0.005$ for mRS 0-2, see Table-2).The effect of glycemic variability on prognosis was neutral (Table II).

The independence of the finding that the first day average blood glucose is a predictor of poor prognosis was examined in various linear regression models and found significant in all of them. For example, in the model extrapolated with the presence of hypertension, the presence of diabetes, NIHSS, age (decade), only the blood glucose average was found to be an independent predictor of poor prognosis (β=-0,155, p=0,045) in addition to NIHSS (β=-0,393, p<0,001).

The incidence rate of any type of hemorrhagic transformation was 27.6% and was associated with the formation of atrial fibrillation only. No difference was observed in terms of glycemia values and variability indexes. In 10 (6.7%) patients with symptomatic intracerebral hemorrhage, the average blood glucose level was 28 mg/dL higher in the first 24 hours ($p=0.045$, see Table III).

DISCUSSION

The high blood glucose level in first 24 hours following the treatment in patients with acute ischemic stroke who were administered with IV tPA adversely affects the third month functional outcome. Out study confirmed multiple studies which reveal and support this idea in the literature [29-31].In the light of this information, it is recommended to keep blood glucose in 140-180

Table I. Clinical response to IV tPA.

	Good response			Dramatic response		
	Yes (n=76)	No (n=69)	*P*	Yes (n=41)	No (n=104)	*P*
Age	69 ± 13	70 ± 13	*0,672*	70 ± 15	69 ± 13	*0,920*
Gender, female	55%	55%	*0,982*	61%	53%	*0,378*
VKİ	27,9 ± 6,1	27,5 ± 5,1	*0,742*	28,6 ± 7,1	27,3 ± 4,8	*0,281*
Hypertension	65%	73%	*0,302*	56%	73%	*0,048*
Diabetes	20%	29%	*0,228*	20%	27%	*0,352*
Atrial fibrillation	29%	38%	*0,264*	29%	35%	*0,538*
Cardioembolism	58%	59%	*0.924*	55%	60%	*0,632*
Symptom-to-door duration (min)	77 ± 40	82 ± 46	*0,691*	91 ± 49	76 ± 39	*0,058*
NIHSS arrival	13,6 ± 5,5	14,7 ± 5, 9	*0,239*	13,2 ± 5,9	14,5 ± 5,6	*0,219*
Symptom-to-needle duration (min)	150 ± 54	171 ± 61	*0,030*	164 ± 67	159 ± 54	*0,626*
Hospitalization duration	16 ± 25	27 ± 28	*0,016*	12 ± 19	25 ± 28	*0,004*
Any hemorrhage	18%	37%	*0,010*	10%	35%	*0,003*
PH2	1%	13%	*0,005*	0%	10%	*0,040*
M1 / TICA / BA occlusion	43%	55%	*0,161*	42%	52%	*0.257*
No occlusion	21%	12%	*0.126*	29%	12%	*0,010*
Parameters of glycemia						
HbA1c	6,14 ± 1,05	6,48 ± 1,32	*0,215*	5,91 ± 0,91	6,45 ± 1,25	*0,057*
Pre-treatment BG	140 ± 57	147 ± 54	*0,497*	139 ± 47	145 ± 58	*0,600*
24-hour average BG	132 ± 45	138 ± 44	*0,451*	125 ± 36	139 ± 47	*0,067*
24-hour BG SD	20,52 ± 26,28	21,97 ± 24,84	*0,742*	20,71 ± 29,98	21,41 ± 23,73	*0,887*
24-hour BG CV	0,18 ± 0,16	0,18 ± 0,14	*0,892*	0,2 ± 0,18	0,17 ± 0,14	*0,326*
J-index	29,25 ± 26,4	28,39 ± 18,28	*0,843*	30,14 ± 25,32	28,43 ± 22,02	*0,735*

Abbreviations; BA: Basilar artery; CV: Coefficient of Variation; Min: Minute; HbA1c:Hemoglobin A1c; ICA:internal carotid artery; IV: Intravenous; BG: Blood Glucose; M1: middle cerebral artery (MCA) first segment; NIHSS: National Institute of Health Stroke Scale; PH2:Parenchymal hematoma type-2; SD:Standard deviation; tPA: tissue plasminogen activator; BMI: Body Mass Index.

Table II. Clinical outcomes with IV tPA.

	Perfect outcome [mRS≤1]			Good outcome [mRS≤2]		
	Yes (n=48)	No (n=96)	*P*	Yes (n=67)	No (n=78)	*P*
Age	65 ± 14	72 ± 12	*0,004*	66 ± 14	72 ± 12	*0,004*
Gender, female	58%	53%	*0,554*	52%	52%	*0,555*
BMI	27,4 ± 5,1	27,9 ± 5,9	*0,658*	29,0 ± 6,9	26,7 ± 4,2	*0,050*
Hypertension	50%	77%	*0.001*	58%	77%	*0,018*
Diabetes	21%	27%	*0,414*	24%	36%	*0.772*
Atrial fibrillation	31%	34%	*0,708*	27%	39%	*0.125*
Cardioembolism	55%	61%	*0.488*	55%	63%	*0.394*
Symptom-to-door duration (min)	83 ± 44	79 ± 43	*0,568*	84 ± 48	77 ± 38	*0,334*
NIHSS arrival	11,8 ± 5,7	15,3 ± 5,4	*<0,001*	11,6 ± 5,3	16,4 ± 5,1	*<0,001*
Symptom-to-needle duration (min)	158 ± 62	162 ± 57	*0,670*	160 ± 62	161 ± 55	*0,845*
Hospitalization duration	10 ± 6	26 ± 31	*0,001*	11 ± 6	30 ± 33	*<0,001*
Any hemorrhage	15%	34%	*0,112*	18%	36%	*0,016*
PH2	0%	10%	*0,020*	0%	13%	*0,002*
M1 / TICA / BA occlusion	40%	53%	*0.125*	39%	57%	*0.028*
No occlusion	23%	14%	*0,155*	20%	14%	*0,411*
Parameters of glycemia						
HbA1c	6 ± 0,84	6,44 ± 1,32	*0,119*	6,13 ± 0,92	6,44 ± 1,4	*0,268*
Pre-treatment BG	132 ± 44	148 ± 60	*0,153*	135 ± 45	151 ± 63	*0,131*
24-hour average BG	121 ± 34	142 ± 48	*0,008*	124 ± 34	145 ± 51	*0,005*
24-hour BG SD	20,8 ± 29,42	21,59 ± 23,65	*0,573*	20,84 ± 26,49	21,79 ± 24,91	*0,830*
24-hour BG CV	0,19 ± 0,18	0,17 ± 0,14	*0,509*	0,18 ± 0,16	0,18 ± 0,15	*0,817*
J-index	26,25 ± 23,4	30,25 ± 22,56	*0,393*	25,82 ± 21,12	31,99 ± 24,09	*0,155*

Abbreviations; BA: Basilar artery; CV: Coefficient of Variation; Min:Minute; HbA1c: Hemoglobin A1c; ICA: internal carotid artery; IV: Intravenous; BG: Blood Glucose; M1: middle cerebral artery (MCA) first segment; NIHSS: "National Institute of Health Stroke Scale"; PH2: Parenchymal hematoma type-2; SD: Standard deviation; tPA: tissue plasminogen activator; BMI: Body Mass Index.

Table III. Post IV tPA hemorrhage.

	Hemorrhage			PH type 2		
	Yes (n=40)	No (n=105)	*P*	Yes (n=10)	No (n=135)	*P*
Age	69 ± 12	70 ± 14	*0,950*	69 ± 14	70 ± 13	*0,845*
Gender, female	63%	53%	*0,294*	50%	56%	*0,718*
BMI	27,1 ± 4,6	27,9 ± 5,9	*0,580*	25,5 ± 4,1	27,9 ± 5,7	*0,284*
Hypertension	73%	67%	*0,522*	60%	69%	*0,549*
Diabetes	28%	24%	*0,624*	20%	25%	*0,723*
Atrial fibrillation	48%	27%	*0,021*	30%	33%	*0,841*
Cardioembolism	63%	56%	*0,477*	50%	59%	*0,614*
Symptom-to-door duration (min)	70 ± 37	85 ± 45	*0,056*	64 ± 39	82 ± 44	*0,194*
NIHSS arrival	15,6 ± 4,7	13,5 ± 6	*0,046*	16,6 ± 4,2	13,4 ± 5,8	*0,143*
Symptom-to-needle duration (min)	157 ± 49	161 ± 61	*0,743*	152 ± 46	161 ± 59	*0,631*
Hospitalization duration	24 ± 26	20 ± 27	*0,367*	35 ± 48	20 ± 24	*0,092*
M1 / TICA / BA occlusion	58%	45%	*0,188*	60%	48%	*0,456*
No occlusion	8%	20%	*0,073*	10%	17%	*0,569*
Parameters of glycemia						
HbA1c	6,48 ± 0,85	6,22 ± 1,24	*0,433*	6,33 ± 0,74	6,27 ± 1,19	*0,923*
Pre-treatment BG	135 ± 35	146 ± 60	*0,347*	153 ± 38	143 ± 56	*0,651*
24-hour average BG	140 ± 31	133 ± 49	*0,342*	161 ± 37	133 ± 45	*0,045*
24-hour BG SD	19,51 ± 23,76	21,9 ± 26,11	*0,628*	24 ± 25,03	21,04 ± 25,54	*0,726*
24-hour BG CV	0,16 ± 0,14	0,18 ± 0,16	*0,578*	0,2 ± 0,16	0,18 ± 0,15	*0,741*
J-index	28,98 ± 17,14	28,72 ± 24,44	*0,958*	38,08 ± 14,54	28,08 ± 23,05	*0,230*

Abbreviations; BA: Basilar artery; CV: Coefficient of Variation; Min: Minute; HbA1c: Hemoglobin A1c; ICA: internal carotid artery; IV: Intravenous; BG: Blood Glucose; M1: middle cerebral artery (MCA) first segment; NIHSS: "National Institute of Health Stroke Scale";PH2: Parenchymal hematoma type-2; SD: Standard deviation; tPA: tissue plasminogen activator; BMI: Body Mass Index.

mg/dL band within the first 24 hours in the guidelines for acute ischemic treatment [32].This is considered as a quality metric.

High blood glucose level is a common incident in the hyperacute period following an ischemic stroke and is considered to be an indicator of acute stress response. Hyperglycemic patients also benefit from IV tPA; however, high level of glucose reduces the effectiveness of thrombolytic therapy [4, 29-31]. In case of high blood glucose, the re-canalization creating and/or enhancing effect of tPA decreases, and a resistance is developed against thrombolytic agent. The first coming the mind out of the factors playing a role here is the the fact that the level of plasminogen activator inhibitor-type 1 (PAI-1) increases due to high blood glucose and hyperinsulism in diabetes and antagonizes tPA. In other words, fibrinolysis decreases in hyperglycemia [33]. Besides, the hyperglycemia directly increasing the coagulation and decreasing penumbral vasodilatation reduces the success of reperfusion. [23] When recanalization and reperfusion are ensured, high blood glucose level and/or its remaining at high levels increases the reperfusion damage and facilitates the development of hemorrhagic complications. Hyperglycemia-induced or increased oxidative stress, lactate accumulation, and tissue acidosis, increased matrix metalloproteinase level may be mediating this effect [23, 34]. On the basis of all these physiopathological logical explanations, we can mention that large scaled studies are required on determination of post-stroke blood glucose target values in hyperacute period, specific to the patients who were administered with IV tPA.

It was observed in our study that the basic glycemic variability parameters and their response to IV tPA are not related. This is not a subject studied in detail in the literature [14, 23]. It was addressed in a study, similar to our finding, that the average blood glucose level is important for the response to IV tPA, however BGSD is not a significant determinant as a GV indicator [35]. In another study, it was reported that J-index values are important in increasing cardiovascular mortality in these patients [20]. Glycemic variability is known to have an effect in a way to increase the vascular complications of diabetes in long term over various mechanisms, particularly oxidative stress [14, 17, 23, 28, 36]. Poor micro- and macrovascular status has the potential to adversely affect the prognosis of acute stroke. On the other hand, in at least three retrospective studies, the positive association between GV and increased mortality in ICU patients were shown to be more prominent in non-diabetic patients [15, 37-39]. In addition, a similar association was also observed in cases with traumatic brain injury [40]. Therefore, the same situation could be expected in

acute stroke cases who were administered with IV tPA, however, this was not supported by initial data. Preferably prospective and large-scale studies in more diverse designs should be planned to elucidate this problem.

Considering the evaluation of our results, it is necessary to address some limitations of our study. First of all, this is a retrospective analysis; a single-center data and the number of patients is "median" for such studies. In addition, the recanalization could not be documented for each patient. Moreover, as "post-stroke" hyperglycemia shows a positive correlation with acute stress response and more importantly with the cerebral infarction size, it was claimed that there is a epiphenomen in terms of prognosis [41]. However, we did not receive neuroimagings for consideration. Most importantly, the number of blood glucose measurements in our study was low and limited to 2-4 measurements in most of the patients. By the increase of this number and periodical checks in certain intervals, basic GV parameters, particularly BG standard deviation, could be more important. Lastly, the nutrition, fluid infusion and insulin administration for the patients were not recorded. Despite all these limitations, our study showed that the high level of blood glucose, rather than variability thereof, has a role on the efficacy of IV tPA. It would be efficient to test this data on a large scale.

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