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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

SERUM ALBUMIN, BILIRUBIN AND PALBI SCORE AND RESPONSE TO INTRAVENOUS THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE

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ABSTRACT

INTRODUCTION: The search for a high utility blood marker in the context of predicting the response to intravenous (IV) thrombolytic therapy in acute ischemic stroke continues. The position of albumin, total bilirubin and PALBI ("Platelet-Albumin-Bilirubin") encountered among the candidate markers has been investigated herein.
METHODS: In a total 156 acute ischemic stroke cases treated with "only" IV tissue plasminogen activator (tPA) (Age: 70 ± 13; Female 58%; NIHSS at admission: 13 ± 5.8), serum levels of albumin and total bilirubin and PALBI score determined before and twenty-four after IV tPA administration to determine their connection to the positive (NIHSS reduction greater than 4 or score becoming 0) and dramatic (NIHSS reduction 8 or more, or score down to 1 or zero) response to tPA, third month good (mRS <=2) or very good (mRS<=1) functional outcome; and development of symptomatic post-tPA intracranial hemorrhagic transformation was determined.
RESULTS: Serum albumin and bilirubin level and PALBI score determined before and after treatment had no effect on positive (51%) or dramatic (29%) response to IV tPA, symptomatic cerebral hemorrhagic transformation (6.4%), any type tPA-related cerebral hemorrhagic changes (25.6%), good (49.4%) and very good (34%) functional outcome in the third month. The tendency of inverse proportion between 24-hour total bilirubin level and very good functional outcome (Beta = -0.039, p = 0.148) and any degree of tPA-related cerebral hemorrhagic transformation (Beta = 0.029, p = 0.161), along with 24th hour serum albumin level and tPA-related any, but not symptomatic, cerebral hemorrhagic transformation (Beta = 0.107, p = 0.047) was disappeared or marginalized when corrected by age and NIHSS.DISCUSSION AND CONCLUSION: In acute ischemic stroke, serum albumin and bilirubin levels measured within the first 24 hours and PALBI score have no modifying role on "effect" and "side-effect" profile of IV tPA therapy.
Keywords: Acute ischemic stroke, thrombolytic, albumin, nutrition, bilirubin, neuroprotection, liver.

AKUT İSKEMİK İNMEDE SERUM ALBUMİN, BİLİRUBİN VE PALBI SKORU VE İNTRAVENÖZ TROMBOLİTİK TEDAVİYE YANIT

ÖZ

GİRİŞ ve AMAÇ: Akut iskemik inmede intravenöz (IV) trombolitik tedaviye yanıtın öngörülebilmesi bağlamında faydalı olabilecek kan belirteci arayışı sürmektedir. Aday belirteçler arasında yer alan albumin, total bilirubin ve PALBI ("Platelet-Albumin-Bilirubin") skorunun konumu tarafımızca araştırılmıştır.
YÖNTEM ve GEREÇLER: Sadece IV doku plazminojen aktivatörü (tPA) ile tedavi edilmiş 156 olguda (Yaş: 70±13 yıl; Kadın %58; NIHSS geliş: 13±5,8) tedavi öncesi ve sonrası 24. saatte ölçülen serum albümin, total bilirubin düzeyi ve PALBI skorunun tPA'ya yanıtın pozitif (NIHSS azalması dörtten fazla veya skor sıfır) ve dramatik (NIHSS azalımı 8 veya daha fazla veya skor 1 veya sıfır), üçüncü ay fonksiyonel sonlanımın iyi (modifiye Rankin skoru-mRS ≤2) veya çok iyi (mRS≤1) olması ve semptomatik post-tPA intrakranial kanama gelişimi ile olan ilişkisi belirlenmiştir.

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BULGULAR: Tedavi öncesi ve sonrası serum albumin ve bilirubin düzeyi ile PALBI skoru, IV tPA'ya pozitif (%51) veya dramatik (%29) cevap, semptomatik kanama (%6,4), IV tPA'ya bağlı kanama (%25,6) üçüncü ay iyi (%49,4) ve çok iyi (%34) fonksiyonel sonuç üzerinde etki yapmamıştır. 24. saat total bilirubin düzeyinin çok iyi fonksiyonel sonlanım (Beta= -0,039, p=0,148) ve herhangi derecede tPA ilişkili kanama (Beta=0,029, p=0,161) ve tedavi sonrası albumin seviyesinin tPA ilişkili kanama (semptomatik kanama değil, Beta=0,107, p=0,047) ile ters orantılı olma eğilimi yaş ve NIHSS ile düzeltilince kaybolmuştur.
TARTIŞMA ve SONUÇ: Akut iskemik inmede ilk 24 saat içindeki serum albumin ve bilirubin düzeyi ile PALBI skorunun IV tPA tedavisinin etki veya yan etkisi profilini modifiye edici etkisi yoktur.
Anahtar Sözcükler: Akut iskemik inme, trombolitik, albumin, nütrisyon, bilirubin, nöroproteksiyon, karaciğer.

INTRODUCTION

Several studies are available about the potential usefulness of serum albumin levels and bilirubin concentrations in predicting the risk and (1-3) etiology (1,4,5) of ischemic stroke and prognosis after acute ischemic stroke (3,6-9). Studies about the potential of serum albumin and bilirubin concentrations to modify clinical outcomes of intravenous [IV] tissue plasminogen activator [tPA] therapy or thrombectomy are very few (10,11). However; in these few studies, serum albumin and bilirubin concentrations have been argued to be the potential predictors of critical outcomes including an increase in symptomatic bleeding rates after IV tPA therapy and (10) increased hemorrhagic transformation and a low functional response after thrombectomy (11). The PALBI ["Platelet-Albumin-Bilirubin"] score; which has been derived from these three parameters and studied as a prognostic marker only in hepatocellular carcinoma so far (12,13), has not been used for prognostication in acute ischemic stroke yet. In this study, we investigated the potential of the PALBI score and its comprising parameters in modifying or showing the effect of IV tPA therapy in acute ischemic stroke.

METHODS

The study was conducted in accordance with the Helsinki Declaration ethical standards and approved by the Hacettepe University Faculty of Medicine Noninterventional Clinical Studies Ethics Committee (Number: 2019/08-43, Date: 07.03.2019).

One hundred fifty-six patients were included; who were recorded in the prospective stroke data bank of Hacettepe University in the last 8 years, who received only IV tPA therapy, and whose serum albümin and bilirubin levels and platelet counts measured before the treatment and in the 24th hour of the treatment were available. The patient inclusion and classification system of our data bank can be found in our previous papers (14-16).

The results of serum albumin and bilirubin levels and platelet count measurements obtained before the treatment and in the 24 hours after the treatment were retrieved. Using these values, the PALBI score was calculated with the following formula:

PALBI score= "2,02 x $\log_{10}$bilirubin-0,37 x (Log_{10}bilirubin)^2 - 0,04 x albümin-3,48 x $\log_{10}$platelet + 1,01 x ($\log_{10}$platelet)^2".

In the formula to calculate the PALBI score; the albumin level is expressed in "gram/L", the bilirubin level is expressed in "microgram/L", and platelet count is expressed in "10^3/microL". PALBI gradients described for hepatocellular carcinoma were not calculated in this study (12).

The United States' National Institutes of Health Stroke Scale (NIHSS) scores before and after the treatment, the length of hospital stay, and the modified Rankin scale [mRS] scores in the third month were retrieved for each patient (17,18). The tPA effect was coded "positive" when the NIHSS score improved more than four points or when a zero score was obtained. The tPA effect was coded "dramatic", when the NIHSS score improved more than eight points or when a score of 1 or lower was obtained. The "good" functional outcome was accepted with mRS scores of ≤2 in the third month and the "very good" clinical outcome was considered with mRS scores of ≤1 (14,16). On the follow-up computed tomography (CT) image [in the 24th hour], "symptomatic post-tPA intracranial hemorrhage" was noted as Fiorelli parenchymal hemorrhage type-2, and any bleeding including the other types of hemorrhage was noted as "any post-tPA hemorrhage" (19).

Statistical Analysis: Values were presented as "mean ± standard deviation", "median ± interquartile range" or "percent" where relevant. After the normality of the data was assessed with the Shapiro-Wilks and Kolmogorov-Smirnov tests, the Student-t or Mann-Whitney U tests were performed to test the numerical values and the chi-square or exact tests were performed for categorical variables. The effects of the studied factors were investigated by creating various logistic experimental models for tPA response, prognosis, and bleeding outcomes. For statistical significance, a p-value of <0.05 was taken at all times. SPSS® for Windows® statistical package program [version 22] was used for the analyses.

RESULTS

Of the 156 patients included in the study [age: 70 ± 13 years; 58% were women; NIHSS score at admission: 13 ± 5.8]; 80 [51%] had a "positive" and 45 [29%] had a "dramatic" response to IV tPA. In the third month, "good" functional outcomes [mRS 0-2] were seen in 49.4% patients, and "very good" outcomes were seen in 34% of the patients. While the frequency of "any bleeding" due to IV tPA is 25.6%, the frequency of the development of "symptomatic PH-type 2 bleeding" is 6.4%.

A positive response to IV tPA therapy showed an increase with a short door-to-needle time [p = 0.008], while a dramatic response showed an increase with the absence of occlusions in CT angiography [p = 0.003] and with the female gender. The albumin and bilirubin levels and PALBI scores before and after the treatment did not modify these obtained responses to IV tPA in the 24th hour [Table I].

The very good functional condition in the third month [mRS 0-1] appeared to be associated with young age [p <0.001], low NIHSS scores [p=0.003], and the absence of occlusions in CT angiography [p=0.089]; while it attracted our attention that, of the studied parameters, the total bilirubin levels in the 24th hour tended to be inversely proportional to very good prognosis [p=0.055, Table II]. However, this potential effect was lost when corrected by age and NIHSS scores [Beta=-0.039, p=0.148]. Good prognosis [mRS 0-2] in the third month showed an increase with young age [p=0.003], low pretreatment NIHSS scores [p<0.001], no major vessel occlusions [p<0.001], or no occlusions at all [p=0.022]. No effects of pretreatment or posttreatment albumin or bilirubin levels or PALBI scores were observed on prognosis [Table II].

No blood parameters were found to be associated with the development of symptomatic bleeding. Although increased posttreatment albumin [about 2 g/L] and total bilirubin [about 2.5 μg/L] levels appeared to be associated with total post-tPA bleeding [p values of 0.019 and 0.056, respectively]; this observed association was either lost [beta=0.029, p=0.161 for bilirubin] or became marginal [beta=0.107 for albumin, p=0.047] when corrected according to NIHSS scores and the vascular condition in regression modeling [Table III].

DISCUSSION AND CONCLUSION

Low serum albumin levels at admission have been associated with poor functional outcomes and increased risk for recurrences in acute ischemic stroke (6,7). This effect can be indirectly related to the nutritional status or the subtype of stroke (1,4). On the other hand, low serum albumin levels in acute stroke have been reported to cause a risk for increased symptomatic hemorrhagic transformation after IV tPA therapy (10). In our study, it has been determined that serum albumin levels measured both before and in the 24th hour after IV tPA therapy did not have a significant effect on prognosis in acute stroke patients.

The risk caused by serum bilirubin levels and the prognostic role of serum bilirubin levels in acute ischemic stroke have not been established, yet (2). It has been stressed that blood levels of bilirubin are associated with neuroprotective or injury-aggravating effects (8,20). It has been suggested that high serum bilirubin levels are protective against atherosclerotic events owing to its potential antioxidant capacity (3). There is available evidence that a high bilirubin level may be related to cardioembolic stroke in acute stroke (5). In our study, no signs have been found out to indicate that total bilirubin levels measured before and in the 24th after IV tPA therapy are significantly involved in the treatment response and emergent risks. However, one study in the literature presented data indicating that increased serum bilirubin levels increased the risk of symptomatic hemorrhagic transformation after thrombectomy in acute ischemic stroke (11).

Other studies have associated high levels of total, direct, and indirect bilirubin with a more severe clinical picture and poor functional outcomes in acute ischemic stroke cases (9,21,22). We have not been able to find any evidence that these observations are valid for patients undergoing thrombolytic therapy. Similarly; we have observed that the PALBI score, which was not studied in stroke previously, does not have an impact on predictions and outcomes in stroke patients, who underwent IV tPA therapy.

In acute stroke; the search for a feasible serum marker continues to be used in the diagnosis and to predict treatment outcomes, treatment risks, complications, or short-term and long-term functional improvement. With a practical and easy bedside marker, a critical step will be taken both for the rapid individualization of treatment and for finding out new treatments in general. In this study, we have determined that serum albumin and bilirubin levels and the PALBI score are not very useful in this respect.

Table I. Response to IV tPA.

tPA Response	Positive	Not positive	p	Dramatic	Not dramatic	p
Age	69.01 ± 14.45	70.16 ± 12.25	*0.595*	70 ± 15.36	69.4 ± 12.58	*0.800*
Female Gender	61%	54%	*0.356*	71%	52%	*0.033*
Pretreatment NIHSS score	12.75 ± 5.6	13.3 ± 6.06	*0.555*	12.62 ± 5.84	13.18 ± 5.82	*0.589*
Door-to-needle time	153.93 ± 56.79	180.03 ± 65.09	*0.008*	167.07 ± 70.26	166.47 ± 58.92	*0.957*
Major vascular occlusion present	44%	49%	*0.537*	40%	49%	*0.326*
No occlusion on CT angiography	25%	16%	*0.154*	36%	15%	*0.003*
Pre-tPA albumin	39.02 ± 4.08	39.1 ± 3.7	*0.892*	38.43 ± 3.76	39.31 ± 3.92	*0.202*
Pre-tPA total bilirubin	9.8 ± 4.79	10.06 ± 5.12	*0.746*	9.33 ± 4.03	10.16 ± 5.26	*0.343*
Pre-tPA thrombocyte count	229.2 ± 78.08	229.83 ± 77.28	*0.960*	235.64 ± 79.78	227.02 ± 76.7	*0.530*
Pre-tPA PALBI score	-2.57 ± 0.46	-2.59 ± 0.38	*0.758*	-2.52 ± 0.52	-2.61 ± 0.38	*0.255*
Post-tPA albumin	36.48 ± 4.1	36.99 ± 4.3	*0.448*	36.03 ± 3.91	37.01 ± 4.29	*0.188*
Post-tPA bilirubin	13.3 ± 6.98	14.73 ± 7.99	*0.233*	12.72 ± 6.07	14.51 ± 7.97	*0.178*
Post-tPA thrombocyte count	213.61 ± 70.73	220.43 ± 67.03	*0.538*	219.67 ± 70.49	215.83 ± 68.42	*0.753*
Post-tPA PALBI score	-2.39 ± 0.36	-2.32 ± 0.3	*0.215*	-2.37 ± 0.38	-2.35 ± 0.31	*0.756*

Note: See the text for abbreviations.

Table II. Functional outcome in the third month.

Modified Rankin Score	mRS 0-1	mRS 2-6	p	mRS 0-2	mRS 3-6	p
Age	64.42 ± 14.96	72.29 ± 11.74	*<0.001*	66.44 ± 14.81	72.71 ± 11.13	*0.003*
Female Gender	59%	56%	*0.794*	56%	58%	*0.754*
Pretreatment NIHSS score	11.11 ± 5.81	13.99 ± 5.59	*0.003*	10.79 ± 5.32	15.18 ± 5.47	*0.000*
Door-to-needle time	164.98 ± 65.28	167.2 ± 60.68	*0.833*	166.99 ± 63.71	165.92 ± 60.86	*0.915*
Major vascular occlusion present	38%	52%	*0.104*	33%	61%	*<0.001*
No occlusion on CT angiography	28%	16%	*0.089*	27%	13%	*0.022*
Pre-tPA albumin	39.61 ± 4.07	38.81 ± 3.77	*0.224*	39.54 ± 3.85	38.64 ± 3.89	*0.146*
Pre-tPA total bilirubin	9.37 ± 4.97	10.06 ± 4.69	*0.390*	9.83 ± 5.02	9.83 ± 4.57	*1.000*
Pre-tPA thrombocyte count	230.92 ± 70.86	228.95 ± 80.81	*0.881*	222.53 ± 67.19	236.53 ± 85.97	*0.260*
Pre-tPA PALBI score	-2.65 ± 0.35	-2.55 ± 0.45	*0.177*	-2.61 ± 0.47	-2.56 ± 0.37	*0.488*
Post-tPA albumin	36.7 ± 4.79	36.75 ± 3.87	*0.951*	36.79 ± 4.37	36.67 ± 4.04	*0.857*
Post-tPA bilirubin	12.36 ± 5.96	14.78 ± 8.05	*0.055*	13.68 ± 6.71	14.22 ± 8.19	*0.650*
Post-tPA thrombocyte count	215.34 ± 60.11	217.83 ± 73.12	*0.831*	209.7 ± 57.05	224.09 ± 78.29	*0.192*
Post-tPA PALBI score	-2.41 ± 0.31	-2.33 ± 0.34	*0.120*	-2.37 ± 0.29	-2.34 ± 0.36	*0.521*

Note: See the text for abbreviations.

Table III. : Bleeding after IV tPA.

tPA-associated bleeding	No bleeding	Bleeding present	P	No symptomatic bleeding	Symptomatic bleeding present	p
Age	69.61 ± 13.94	69.75 ± 12.03	*0.956*	69.62 ± 13.48	70 ± 13.52	*0.932*
Female Gender	60%	57%	*0.732*	50%	58%	*0.611*
Pretreatment NIHSS score	12.34 ± 6.06	14.88 ± 4.63	*0.017*	12.83 ± 5.83	15.4 ± 5.3	*0.177*
Door-to-needle time	170.76 ± 67.65	152.95 ± 39.93	*0.118*	167.1 ± 63.05	153 ± 46.56	*0.489*
Major vascular occlusion present	60%	42%	*0.066*	60%	46%	*0.387*
No occlusion on CT angiography	8%	24%	*0.023*	20%	20%	*0.992*
Pre-tPA albumin	38.99 ± 4.07	39.23 ± 3.37	*0.738*	39.1 ± 3.89	38.35 ± 4.11	*0.557*
Pre-tPA total bilirubin	9.43 ± 4.7	10.87 ± 4.96	*0.101*	9.83 ± 4.89	9.3 ± 3.32	*0.736*
Pre-tPA thrombocyte count	228.75 ± 76.55	231.98 ± 80.68	*0.821*	228.1 ± 78.47	251.2 ± 57.99	*0.363*
Pre-tPA PALBI score	-2.61 ± 0.44	-2.53 ± 0.34	*0.327*	-2.59 ± 0.43	-2.51 ± 0.3	*0.537*
Post-tPA albumin	36.29 ± 4.38	38.09 ± 3.3	*0.019*	36.75 ± 4.29	36.77 ± 2.45	*0.986*
Post-tPA bilirubin	13.23 ± 7.18	15.86 ± 8.12	*0.056*	13.99 ± 7.58	12.62 ± 6.27	*0.577*
Post-tPA thrombocyte count	216.88 ± 72.06	217.2 ± 59.19	*0.980*	215.32 ± 69.07	241 ± 63.08	*0.255*
Post-tPA PALBI score	-2.37 ± 0.33	-2.35 ± 0.35	*0.755*	-2.36 ± 0.33	-2.35 ± 0.4	*0.891*

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Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Faculty of Medicine Noninterventional Clinical Studies Ethics Committee (Number: 2019/08-43, Date: 07.03.2019).

Informed Consent: It was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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