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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

THE EFFECT OF LIPOPROTEIN(A) LEVEL ON THE EFFICIENCY AND SAFETY OF INTRAVENOUS THROMBOLYTIC THERAPY

Ezgi YILMAZ[1], Elif SARIÖNDER GENCER[2], Ethem Murat ARSAVA[1], Mehmet Akif TOPÇUOĞLU[1]

[1]Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, TÜRKİYE
[2]Health Sciences University Antalya Training and Research Hospital, Neurology Clinic, Antalya, TÜRKİYE

ABSTRACT

INTRODUCTION: Increased lipoprotein(a) (Lp(a)) is an atherosclerotic cardiovascular disease risk factor that has the potential to be used in clinical practice. Antifibrinolytic effects have been reported due to its structural similarity with plasminogen. In our study, the effect of Lp(a) level on the response to intravenous tissue plasminogen activator(iv tPA) in acute ischemic stroke was investigated.
METHODS: Among the patients evaluated at Hacettepe University Hospital in the last 15 years, those who received tPA treatment and had Lp(a) levels checked within 72 hours were reviewed in terms of tPA efficacy, prognosis and hemorrhagic transformation. Response to iv tPA treatment was divided into 2 categories according to NIHSS decrease at 24 hours (effective response: decrease of at least 4 points or zero, dramatic response: decrease of at least 8 points or zero or one) 0 and 1 were rated as 'excellent outcome', 0, 1, and 2 were rated as 'good outcome' according to the modified Rankin score (mRS) evaluated at 3 months. IV tPA-related hemorrhagic transformation was evaluated according to Fiorelli's classification.
RESULTS: 203 patients (mean age 71±14;108 women) with iv tPA treatment; an 'effective response' was observed in 46% and a 'dramatic response' was observed in 29%. According to the mRS of the patients at 3 months, 33% had an excellent outcome and 51% had a good outcome. After IV tPA treatment; cerebral hemorrhage of any severity in 19% of patients; parenchymal hematoma type 2 was detected in 5% of them. In analyzes performed according to prognosis, iv tPA response and post-tPA cerebral hemorrhage status, there was no difference in Lp(a) level and the frequency of subgroups (>30 mg/dl, >60 mg/dl, >100 mg/dl) formed with three different cut-off values.
DISCUSSION AND CONCLUSION: The results of our study suggested that the antifibrinolytic effect due to Lp(a) was so low that it did not affect the tPA activity. Prospective studies with larger participation are needed to better demonstrate this antifibrinolytic effect, which is thought to be weak.
Keywords: Lipoprotein(a), tissue plasminogen activator, acute ischemic stroke.

Address for Correspondence: Ezgi Yılmaz, MD. Hacettepe University Faculty of Medicine, Department of Neurology, 06100, Sıhhıye, Ankara, Türkiye
Phone: +90312 305 18 06 **E-mail:** igezgi@hotmail.com
Received: 10.05.2022 **Accepted:** 20.09.2022
ORCID IDs: Ezgi Yılmaz 0000-0002-9082-1034, Elif Sarıönder Gencer 0000-0003-3881-9559, Ethem Murat Arsava 0000-0002-6527-4139, Mehmet Akif Topçuoğlu 0000-0002-7267-1431.
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İNTRAVENÖZ TROMBOLİTİK TEDAVİ ETKİNLİK VE GÜVENİLİRLİĞİNE LİPOPROTEİN(A) DÜZEYİNİN ETKİSİ

ÖZ

GİRİŞ ve AMAÇ: Lipoprotein(a) (Lp(a)) yüksekliği klinik pratikte kullanılabilme potansiyeline sahip bir aterosklerotik kardiyovasküler hastalık risk faktörüdür. Yapısal olarak plazminojenle gösterdiği benzerlik nedeni ile antifibrinolitik etkileri bildirilmiştir. Çalışmamızda Lp (a) düzeyinin, akut iskemik inmede intravenöz doku plazminojen aktivatörüne (iv tPA) yanıta olan etkisi incelenmiştir.

YÖNTEM ve GEREÇLER: Son 15 yıl içerisinde Hacettepe Üniversitesi Hastanesi'nde değerlendirilen IV tPA tedavisi almış ve 72 saat içinde bakılmış Lp(a) düzeyi olan hastalar tPA etkinliği, prognoz ve hemorajik transformasyon açısından incelendi. NIHSS'de 24. saatte en az 4 puan azalma ve ya sıfıra düşme iv tPA tedavisine 'etkin cevap'; 8 puan ya da daha fazla azalma ve ya sıfır ya da bire düşme 'dramatik cevap' olarak kategorize edildi. Üçüncü ayda değerlendirilen modifiye Rankin skoru'na (mRS) göre 0 ve 1 'mükemmel sonlanım'; 0, 1 ve 2 'iyi sonlanım' olarak değerlendirildi. IV tPA ilişkili hemorajik transformasyon Fiorelli's sınıflamasına göre değerlendirildi.

BULGULAR: 203 hastanın (yaş ortalaması 71±14; 108 kadın) %46'sında iv tPA tedavisi ile 'etkin cevap', %29'unda 'dramatik cevap' izlendi. Hastaların 3. aydaki mRS'larına göre %33'ünde mükemmel sonlanım, % 51'inde iyi sonlanım olduğu gözlendi. İv tPA tedavisi sonrası hastaların %19'unda herhangi bir ağırlıkta serebral hemoraji saptanırken; %5'inde parankimal hematom tip 2 saptandı. Prognoz, iv tPA cevabı ve tPA sonrası serebral hemoraji durumuna göre yapılan analizlerde Lp(a) düzeyi ve üç farklı kesim değeri ile oluşturulan subgrupların (>30 mg/dl, >60 mg/dl, >100 mg/dl) sıklığı açısından bir farklılık saptanmadı.

TARTIŞMA ve SONUÇ: Çalışmamızın sonuçları Lp(a) ya bağlı antifibrinolitik etkinin tPA etkinliğini etkilemeyecek kadar düşük seviyede olduğunu düşündürmüştür. Zayıf olduğu düşünülen bu antifibrinolitik etkinin daha iyi ortaya konulabilmesi daha geniş katılımlı prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Lipoprotein(a), doku plazminojen aktivatörü, akut iskemik inme.

INTRODUCTION

Lipoprotein(a) [Lp(a)] is an atherosclerotic cardiovascular disease risk factor that can also be used in clinical practice (1). Lp(a) is a complex molecule and consists of a cholesterol-loaded low-density lipoprotein (LDL)-like moiety, a plasminogen-like glycoprotein named apolipoprotein(a), and a covalently bound apolipoprotein B (2). The LDL-like portion is responsible for increased atherogenic risk as it is more prone to oxidation and foam cell formation than LDL through endothelial penetration. Due to its molecular homology to plasminogen, apolipoprotein(a) competes for plasminogen binding sites on endothelial cells, resulting in inhibition of fibrinolysis and increased thrombogenic risk (3). Several studies have associated increased Lp(a) level with decreased clot permeability and prolonged fibrin lysis time (4-6). Despite conflicting results in the literature regarding the relationship between acute ischemic stroke and Lp(a), large-scale studies have shown that this association is stronger in patients under 60 years of age with large vessel atherosclerosis and in African Americans (7, 8).

Intravenous (IV) recombinant tissue plasminogen activator (tPA) therapy is an approved treatment in patients with acute ischemic stroke, and it was licensed with this indication in Turkey in 2006 and used as a part of routine treatment (9, 10). This study evaluated the possible effect of Lp(a) level on IV tPA treatment response, prognosis and complications based on its potential antifibrinolytic properties.

METHODS

A total of 203 patients (mean age 70.5 ± 14.3; 108 women) who received IV tPA treatment without mechanical thrombectomy in the last 15 years at the stroke units of Hacettepe University and had Lp(a) levels checked within 72 hours were evaluated for IV tPA efficacy, prognosis and intracerebral hemorrhage. The study was performed retrospectively from the prospectively created stroke database. Approval was obtained from the Hacettepe University Non-Invasive Clinical Research Ethics Committee for the project plan (Date: 19.04.2022, No: 2022/07-39) and stroke database (Date: 19.04.2022, No: 2022/07-48). The study was conducted in accordance with

the ethical standards of the Declaration of Helsinki.

All patients underwent routine cardiac and vascular evaluation to determine the etiology of stroke and were categorized according to the "The Causative Classification of Stroke System (CCS)" stroke classification (11).

Stroke severity was measured with the NIHSS (12) assessed at admission, at the 24th hour of IV tPA, and at discharge. The level of disability of the patients was determined by the Modified Rankin Scale (13) at the 3rd month. In the NIHSS scale, a reduction of at least 4 points or a decrease to zero at 24 hours was considered an 'effective response' to IV tPA treatment, a reduction of 8 points or more or a decrease to zero or one was considered 'dramatic response'. In the mRS scale evaluated at 3 months, 0 and 1 were considered 'excellent outcome' and 0, 1 and 2 were considered 'good outcome' (14, 15).

Cerebral hemorrhage, one of the complications of IV tPA treatment, was evaluated according to Fiorelli's classification, dividing control non-contrast brain computed tomography (CT) findings at 24-36 hours into 5 categories: no hemorrhagic transformation, hemorrhagic infarct-1(HI-1), hemorrhagic infarct-2 (HI-2), parenchymal hematoma-1 (PH-1), parenchymal hematoma-2 (PH-2). Since PH-2 is associated with early neurological deterioration and 3-month mortality, unlike other categories, patients in this category were also evaluated separately (16).

In the first 72 hours, Lp(a), LDL, HDL (high-density lipoprotein), triglyceride, HbA1c values were measured in the morning after at least 8 hours of fasting. Due to the high variation of Lp(a) levels among individuals, values were evaluated using different cut-off values such as > 30 mg/dl, > 60 mg/dl, > 100 mg/dl.

Statistical Analysis: All data were expressed as mean ± standard deviation, median (minimum - maximum), mean (95% confidence interval), and percentage according to their characteristics. The normal distribution was evaluated with the Kolmogorov-Smirnov or ShapiroWilks test depending on the data. Mann-Whitney U/ Student-t test and Chi-square / "exact" test were used to assess the difference between the groups according to the structure of the data and groups. $p < 0.05$ was considered statistically significant. Analyses were performed using the SPSS version 22 software package.

RESULTS

Among 203 patients, the etiologic cause according to CSS was cardioembolism in 37.9%, cryptogenic embolism in 28.6%, other causes in 2%, unclassifiable in 4.9%, small vessel disease in 4.4%, cryptogenic in 11.3%, large vessel atherosclerosis in 6.4%, and incomplete evaluation in 4.5%.

After IV tPA treatment, 46% of the patients had 'effective response' and 29% had 'dramatic response'. Patients in the effective response group were compared with those without an effective response in terms of sociodemographic, clinical and laboratory parameters. The incidence of hypertension (HT), the time between symptom onset and IV tPA, the incidence of cerebral hemorrhage, and the length of hospital stay were statistically significantly less in the effective response group. Analysis of the same parameters in the dramatic response group patients revealed statistically significantly lower HbA1c values, HT incidince and length of hospital stay. According to the Lp(a) level categories with 3 different cut-off values, there was no significant difference between the patient groups with effective response and dramatic response compared to those without response (Table 1).

According to the patients' mRS at 3 months, 33% had an excellent outcome, and 51% had a good outcome. The parameters of age, admission NIHSS, HT incidence, presence of cerebral hemorrhage and length of stay were statistically significantly lower in both groups. There was no significant difference between excellent and good outcome groups according to 3 different Lp(a) level cut-off values (Table 2).

After IV tPA treatment, cerebral hemorrhage of any severity was detected in 19%, and parenchymal hematoma Type 2 was observed in 5% of the patients. While the length of hospital stay was statistically significantly longer in both groups, the incidence of atrial fibrillation, admission NIHSS score, incidence of cardioembolism, and HbA1c were statistically significantly higher in any cerebral hemorrhage group. There was no significant difference in the groups with cerebral hemorrhage and parenchymal hematoma Type 2 according to the Lp(a) categories with 3 different cut-off values (Table 3).

Table 1. Intravenous tPA therapy response.

	Effective Response			Dramatic Response		
	Yes (n=94)	No (n= 108)	p	Yes (n=59)	No (n=143)	p
Age	71±15	70±14	0.711	71±15	70±14	0.788
Female	55%	52%	0.622	58%	%52	0.446
BMI	28.3±6.3	26.9±4.2	0.480	28.4±6.6	27.3±4.8	0.628
HT	**64%**	**77%**	**0.042**	**59%**	**76%**	**0.021**
DM	26%	28%	0.719	19%	30%	0.095
AF	19%	27%	0.196	19%	25%	0.318
Admission NIHSS	13±6	12±6	0.817	13±6	12±6	0.606
Symptom onset-tPA time (min)	**161±60**	**187±67**	**0.001**	168±63	177±65	0.175
Hemorrhage	**11%**	**27%**	**0.004**	9	24	0.12
Length of Stay	**12±16**	**21±22**	**<0.001**	**11±18**	**19±20**	**< 0.001**
Cardioembolism	46%	47%	0.886	44%	48%	0.713
Large Vessel Atherosclerosis	7%	6%	0.585	5%	7%	0.760
Small vessel disease	2%	7%	0.135	2%	6%	0.289
Lp (a) (mg/dl)	37±42.3	34.3±33.4	0.905	36.6±44.7	35.1±34.6	0.838
Lp (a)>30 mg/dl	44%	42%	0.78	44%	42%	0.783
Lp (a) >60mg/dl	23%	22%	0.98	22%	23%	0.985
Lp (a) >100mg/dl	7%	6%	0.788	7%	7%	1
HbA1c	6.2±1.3	6.7±1.7	0.139	**5.9±1.3**	**6.6±1.6**	**0.020**
LDL	123±38.3	123.8±34.2	0.688	122.5±39.5	123.7±34.7	0.354
Triglyceride	122.1±77.6	126±73.9	0.628	123.8±55.6	124.4±82.1	0.432
HDL	43±10.6	44.5±13.1	0.756	43.8±10.8	43.8±12.5	0.871

Abbreviations: VKİ: BMI: Body Mass Index, HT: Hypertension, DM: Diabetes Mellitus, AF: Atrial Fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, LP (a): Lipoprotein (a), LDL: Low Density Lipoprotein , HDL: High Density Lipoprotein HbA1c: Hemoglobin A1c.

Table 2. Prognosis.

	Excellent Outcome			Good Outcome		
	Yes (n=67)	No (n=136)	p	Yes (n=104)	No (n=99)	p
Age	**65±15**	**73±13**	**<0.001**	**66±15**	**75±12**	**<0.001**
Female	52%	54%	0.847	48%	59%	0.134
BMI	28.8±5.8	27.2±5.3	0.117	28.7±6.6	26.7±3.7	0.276
HT	**54%**	**79%**	**<0.001**	**64%**	**79%**	**0.016**
DM	21%	30%	0.163	24%	30%	0.315
AF	16%	27%	0.11	17%	29%	0.043
Admission NIHSS	**10±6**	**14±6**	**<0.001**	**10±6**	**15±6**	**<0.001**
Symptom onset-tPA time (min)	171±63	177±66	0.573	170±58	180±71	0.342
Hemorrhage	**9%**	**24%**	**0.009**	**13%**	**26%**	**0.013**
Length of Stay	**8±6**	**21±23**	**<0.001**	**9±8**	**25±25**	**<0.001**
Cardioembolism	42%	44%	0.485	47%	47%	0.991
Large Vessel Atherosclerosis	8%	6%	0.762	6%	7%	0.705
Small vessel disease	6%	4%	0.481	4%	5%	0.743
Lp (a) (mg/dl)	36.6±43.1	34.8±34.9	0.995	39±42.6	31.6±31.5	0.349
Lp (a)>30 mg/dl	45%	41%	0.626	46%	38%	0.263
Lp (a) >60mg/dl	23%	22%	0.936	25%	19%	0.320
Lp (a) >100mg/dl	8%	7%	0.777	8%	6%	0.647
HbA1c	6.3±1.8	6.5±1.4	0.153	6.3±1.5	6.6±1.5	0.055
LDL	**126±41.4**	**122.8±34**	**0.047**	127.6±38.9	119.9±33.6	0.098
Triglyceride	127.9±59.6	122.9±82	0.185	123.8±58.6	125.3±89.8	0.316
HDL	42.5±11.4	44.5±12.2	0.214	43.6±12.1	44±11.9	0.687

Abbreviations: BMI: Body Mass Index, HT: Hypertension, DM: Diabetes Mellitus, AF: Atrial Fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, LP (a): Lipoprotein (a), LDL: Low Density Lipoprotein , HDL: High Density Lipoprotein , HbA1c: Hemoglobin A1c.

Considering the studies that have documented more prominent Lp(a) elevation in the group under 60 years of age and with large vessel atherosclerosis, the analyses were repeated for these subgroups. However, these analyses revealed no statistically significant difference between IV tPA response, prognosis and post-IV tPA hemorrhage groups according to the Lp(a) categories with 3 different cut-off values (data not presented).

Table 3. Cerebral hemorrhage after intravenous tPA.

	Cerebral Hemorrhage			Parenchymal Hematoma Type 2		
	Yes (n=39)	No (n=164)	p	Yes (n=11)	No (n=192)	p
Age	72±13	70±15	0.593	73±14	70±15	0.556
Female	62%	51%	0.246	55%	53%	0.927
BMI	27.5±5.2	27.7±5.5	0.871	27.1±1.8	27.7±5.5	0.786
HT	69%	71%	0.794	64%	71%	0.733
DM	31%	26%	0.566	36%	27%	0.493
AF	**41%**	**19%**	**0.003**	18%	23%	1
Admission NIHSS	**15±6**	**12±6**	**0.010**	16±6	12±6	0.072
Symptom onset-tPA time (min)	167±50	177±67	0.631	158±51	176±65	0.437
Hemorrhage	**24±19**	**15±20**	**<0.001**	**34±30**	**16±19**	**0.012**
Length of Stay	**63%**	**42%**	**0.038**	29%	47%	0.450
Cardioembolism	3%	7%	0.469	9%	6%	0.526
Large Vessel Atherosclerosis	0%	6%	0.211	0%	5%	1
Small vessel disease	35.1±36.6	35.5±38	0.712	26.2±31.3	35.9±38	0.334
Lp (a) (mg/dl)	41%	43%	0.851	36%	43%	0.763
Lp (a)>30 mg/dl	23%	22%	0.908	9%	23%	0.462
Lp (a) >60mg/dl	8%	7%	0.735	9%	7%	0.554
Lp (a) >100mg/dl	**6.6±0.9**	**6.4±1.6**	**0.048**	6.6±0.8	6.4±1.6	0.220
HbA1c	117.5±33	125.4±37.2	0.324	120.2±40.3	124±36.4	0.514
LDL	110.1±41.2	128.1±81.3	0.505	121.1±52.1	124.7±76.7	0.865
Triglyceride	46.5±15.9	43.2±10.8	0.264	45.3±10.4	43.7±12.1	0.369

Abbreviations: BMI: Body Mass Index, HT: Hypertension, DM: Diabetes Mellitus, AF: Atrial Fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, LP (a): Lipoprotein (a), LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein), HbA1c: Hemoglobin A1c.

DISCUSSION AND CONCLUSION

Literature on the effects of Lp(a) level on the fibrinolytic system contains conflicting data. Treatments that can significantly lower Lp(a) levels have paved the way for human evaluation of the antifibrinolytic effects of Lp(a). A randomized controlled trial with Apo(a)-directed Antisense Oligonucleotide [IONIS-APO(a)Rx] showed no change in clot lysis time or markers of coagulation and fibrinolysis with lowering of Lp(a). The same study found no change in clot lysis parameters evaluated ex vivo at increasing levels of Lp(a) from 12.5 nmol/l to 200 nmol/l in control experiments (17). This suggests that the tPA-plasminogen-fibrin relationship is not affected by the high Lp(a) level. Other studies in which IV tPA therapy was given for myocardial infarction supported these findings. Lp(a) level did not affect the success of thrombolysis (18,19). A recent study evaluated clot lysis time at different tPA concentrations at low (0-20 mg/dl), moderate (21-66 mg/dl), and high (> 66 mg/dl) Lp(a) levels and concluded that increased Lp(a) levels do not cause prolongation of clot lysis time (20). Clinical and preclinical studies have also emphasized the strong effect of Lp(a) on fibrinolysis (4-6,21). In patients with severe aortic stenosis, Lp(a) was shown to prolong fibrin lysis, as assessed by CLT2018 (21). Since these studies were conducted in the same laboratory, they must first be confirmed by other Laboratories (20). A decrease in Lp(a) level, which starts within 12 hours and lasts up to 72 hours, has been detected in patients given IV tPA treatment for unstable angina pectoris. After 72 hours, Lp(a) returns to its basal value. This is attributed to the increased binding of Lp(a) to intravascular fibrinogen and fibrin via plasmin (22). In our study, no correlation was found between Lp(a) level and IV tPA response, prognosis, and cerebral hemorrhage after IV tPA. Our study is noteworthy because it clinically supports the findings of in vitro studies in the literature.

Our study has some limitations. Due to the small sample size, it was not possible to exclude the presence of correlation completely. Besides, the measurement times of Lp(a) levels differed between patients. Although Lp(a) level is known to be relatively stable, it may have affected the results due to its acute phase reactant feature. In our study, Lp(a) level was presented by mass as mg/dl. This brings forward isoform sensitivity, as all particle content (apo (a), apoB-100, cholesterol, cholesterol ester, phospholipid, triglyceride and carbohydrate) were included in the measurement (23,24).

The results of our study suggest that the antifibrinolytic effect modification due to Lp(a) is too small to affect the efficacy of IV tPA. In order to

better demonstrate this antifibrinolytic effect, which is thought to be weak, prospective studies with larger sample size in cohorts containing different races and follow-up measurements with isoform-sensitive methods are needed.

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Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Non-Invasive Clinical Research Ethics Committee (Date: 19.04.2022, No: 2022/07-39.

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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