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Relationship between blood pressure levels during thrombolytic therapy and functional outcomes in patients with middle cerebral artery infarction

Orta serebral arter enfarktüslü hastalarda trombolitik tedavi sırasındaki kan basıncı düzeyleri ile fonksiyonel sonuçlar arasındaki ilişki

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Abstract

Aim: Previous studies have investigated the relationship between blood pressure (BP) level before and after intravenous (IV) thrombolytic therapy, and functional outcomes of acute ischemic stroke (AIS). However, the relationship between BP level during thrombolytic infusion and functional outcomes has not been well studied. Therefore, in this study, we investigated the relationship between BP levels during thrombolytic therapy and functional outcomes at the 3rd month in AIS patients with middle cerebral artery (MCA) infarction.

Methods: This case-control study was conducted on 60 patients with infarcts in more than 1/3 of MCA. Among these, 20 patients underwent IV thrombolytic therapy after giving informed consent (study group). Forty patients who did not receive thrombolytic therapy were included in the control group. Patients undergoing IV thrombolytic therapy were divided into two groups according to modified Rankin Scale (mRS) at the 3rd month: Those with good functional outcomes (mRS score=0–2) and poor functional outcome (mRS score=3–6).

Results: The poor functional outcome group had a higher mean diastolic BP than the good functional outcome group (P=0.01). Systolic BP was <140 mmHg and diastolic BP was <75 mmHg in the good functional outcome group. A significant, positive, and moderate correlation was found between the mRS score and diastolic BP at the time of admission to the emergency department (r=0.679, P=0.001), immediately before (r=0.580, P=0.007), and during IV thrombolytic therapy (r=0.643, P=0.002).

Conclusion: In AIS patients with MCA infarction, high diastolic BP levels during IV thrombolytic therapy are associated with poor functional outcomes.

Keywords: Acute ischemic stroke, Blood pressure, Intravenous thrombolytic therapy, Middle cerebral artery infarction, Functional outcomes, Modified Rankin scale

Öz

Amaç: Önceki çalışmalar, intravenöz (IV) trombolitik tedavi öncesi ve sonrası kan basıncı (KB) düzeyi ile akut iskemik inme (Aİİ)'nin fonksiyonel sonuçları arasındaki ilişkiyi araştırmıştır. Bununla birlikte, trombolitik infüzyonu sırasındaki KB düzeyi ile fonksiyonel sonuçlar arasındaki ilişki iyi araştırılmamıştır. Bu nedenle, bu çalışmada orta serebral arter (MCA) enfarktüslü Aİİ hastalarında trombolitik tedavi sırasındaki KB düzeyleri ile 3.'üncü aydaki fonksiyonel sonuçlar arasındaki ilişki araştırıldı.

Yöntemler: Bu vaka-kontrol çalışması, MCA'nın 1/3'ünden daha büyük enfarktüsü olan 60 hasta üzerinde gerçekleştirildi. Bunlardan 20'si aydınlatılmış onam alındıktan sonra IV trombolitik tedavi yapılmış hastalardı (çalışma grubu). Trombolitik tedavisi yapılmayan 40 hastada da kontrol grubu olarak alındı. IV trombolitik tedavi yapılan hastalar 3.'üncü aydaki modifiye Rankin Skalasına (mRS) göre iki gruba ayrıldı: iyi fonksiyonel sonuç (mRS skoru=0-2) ve kötü fonksiyonel sonuç (mRS skoru=3-6).

Bulgular: Kötü fonksiyonel sonuç grubu iyi fonksiyonel sonuç grubuna göre daha yüksek ortalama diyastolik KB'ye sahipti (P=0,01). İyi fonksiyonel sonuç grubunda sistolik KB <140 mmHg ve diyastolik KB <75 mmHg idi. Acil servise girişteki (r=0,679; P=0,001), IV trombolitik infüzyonundan hemen önceki (r=0,580; P=0,007) ve infüzyon sırasındaki ortalama diyastolik KB düzeyleri (r=0,643; P=0,002) ile mRS arasında anlamlı, pozitif ve orta düzeyde bir korelasyon vardı.

Sonuç: MCA enfarktüslü Aİİ hastalarında, IV trombolitik tedavi sırasındaki yüksek diyastolik KB düzeyleri kötü fonksiyonel sonuçlarla ilişkilidir.

Anahtar kelimeler: Akut iskemik inme, Kan basıncı, İntravenöz trombolitik tedavi, Orta serebral arter enfarktüsü, Fonksiyonel sonuçlar, Modifiye Rankin skalası

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Introduction

Alteplase, a recombinant tissue plasminogen activator, is used in intravenous (IV) thrombolytic therapy for the treatment of acute ischemic stroke (AIS) [1]. Although there are certain limitations to its use, e.g., blood pressure (BP), and some negative treatment outcomes, it has become important in the treatment of AIS in recent years [2,3]. Regardless of whether mechanical thrombectomy is performed, IV thrombolytic therapy is the first-line treatment that should be administered to patients who meet the treatment criteria [3]. The American Heart Association/American Stroke Association (AHA/ASA) guidelines [3] specify that one of the criteria for commencing IV thrombolytic therapy is a systolic BP of <185 mmHg and diastolic BP of <110 mmHg because BP slightly below these values may negatively affect prognosis. A meta-analysis showed that high pre-thrombolysis systolic BP was associated with worse outcomes in thrombolysed patients with acute ischemic stroke [4]. For ensuring good prognosis in patients undergoing IV thrombolytic therapy, it may be better to maintain BP within the normal limits accepted by international standards during the therapy [5].

Stroke severity, atrial fibrillation, coronary artery disease, diabetes mellitus, pneumonia and advanced age are known to be poor prognostic factors for AIS [6]. However, the relationship between blood pressure and functional outcomes during IV thrombolytic therapy infusion has not been well studied. The aim of the present study was to investigate the relationship between BP levels during IV thrombolytic therapy and functional outcomes in patients who developed an infarct in more than 1/3 of the MCA irrigation area.

Materials and methods

Study population

This retrospective case-control study was conducted on patients with MCA infarction treated at Aksaray University Training and Research Hospital between December 2016 and March 2019. A total of 60 patients with MCA infarction who were clinically eligible for IV thrombolytic therapy [National Institutes of Health Stroke Scale (NIHSS) of ≥5 or presence of aphasia or homonymous hemianopsia] were included in the study. Among these, 20 patients underwent IV thrombolytic therapy after giving informed consent (study group), and 40 patients who did not receive thrombolytic therapy due to contraindications were included in the control group. These patients were treated with non-thrombolytic treatment methods (antiaggregants and/or anticoagulants).

Generally, in the emergency department of our hospital, anamnesis is first obtained from patients presenting with a preliminary diagnosis of stroke or from their relatives. The onset time of symptoms, time of arrival to the emergency department, and time of IV thrombolytic therapy administration are routinely recorded. Vital signs (BP, fever, pulse, and arterial oxygen saturation) are rapidly measured, and blood glucose measurement is performed using a fingerstick. During rapid neurological examination, blood samples are concurrently collected for hemogram, activated partial thromboplastin time (aPTT), international normalized ratio (INR), and biochemical analyses. Brain computed tomography or magnetic resonance imaging is performed for brain parenchymal imaging. In patients with an indication for IV thrombolytic therapy after the diagnosis of AIS, based on neurological examination and brain imaging, and in case of no contraindications, alteplase was intravenously administered at a dose of 0.9 mg/kg (maximum dose: 90 mg/kg; 10% of the total dose via IV bolus and the remaining dose via 1-h infusion) after obtaining informed consent [1,3]. In all patients with AIS, BP measurement, vital signs monitoring, and neurological evaluation are performed before IV thrombolytic therapy, every 15 min during the therapy, every 30 min within 6 h after the therapy, and every 60 min between 6 and 24 h. The modified Rankin Scale (mRS) score and other clinical findings are routinely recorded in our database before discharge and at the 3-month follow-up.

The hospital database was used to obtain information regarding the patients' BP measured at the time of admission to the emergency department, immediately before IV thrombolytic therapy, and every 15 min during the therapy, pre-treatment and 3-month mRS scores, baseline NIHSS scores, symptom-to-door, door-to-needle, and onset-to-needle times, Alberta Stroke Program Early Computed Tomography Score scores, clinical and laboratory findings, risk factors and other demographic characteristics. This information was recorded for statistical analysis. Patients with incomplete data and those aged <18 years were excluded.

The mRS, the most used outcome measure for post-stroke disability rating, is scored from 0 to 6 as follows: 0-No symptoms. 1-No obvious disability, despite the symptoms, the patient can perform daily activities and duties. 2- Mild disability, he cannot do all the usual tasks and activities he did in the past, but he can do his own work without help. 3- Moderate disability, he needs partial help to do his own work, but he can walk on his own without help. 4-Severe disability, unable to walk without help and meet physical needs. 5-Very severe disability, bed-dependent, incontinent, and needing constant care, and attention. 6- It is defined as "death" [7,8]. The functional outcomes of the study patients were evaluated with mRS scores at the 3rd month. Patients undergoing IV thrombolytic therapy were divided into two groups according to their 3-month mRS score: Good functional outcome (mRS score: 0–2) and poor functional outcome (mRS score: 3–6) [9,10].

The study was approved by the Aksaray University Human Research Ethics Committee (4/24/2020, 2020/03-66) and conducted in compliance with the Declaration of Helsinki.

Statistical analysis

The normality of continuous variables was investigated using the Shapiro–Wilk test. Descriptive statistics are expressed as mean, standard deviation, median, and minimum-maximum. Non-parametric statistical methods were used for values with skewed distribution. Mann–Whitney U-test was used for the comparison of two non-normally distributed independent groups. Fisher's exact test was used for categorical variables, and the results are expressed as count (and percentages). A two-sided *P*-value <0.05 was considered statistically significant. Spearman's rho correlation coefficient was used to investigate the relationship among non-normally distributed parameters. Statistical analysis was performed using the MedCalc Statistical

Software (version 12.7.7; MedCalc Software bvba; Ostend, Belgium; http://www.medcalc.org; 2013).

Results

As shown in Table 1, the mean age of the study and control group were 62.8 and 75.1 years, respectively. A significant difference was observed between these two groups in terms of age and baseline NIHSS scores (P=0.003), with the mean age being higher and baseline NIHSS score being lower in the control group. There were no significant differences between these groups in terms of hypertension (P=0.481), diabetes mellitus (P=0.560), hyperlipidemia (P=0.136), atrial fibrillation (P=0.154), coronary artery disease (P=0.753), congestive heart failure (P=0.165), heart valve disease (P=1.000), stroke and transient ischemic attack history (P=0.707) and gender (P =1.000). Among the patients clinically eligible for IV thrombolytic therapy (n=60), 33.33% were treated with alteplase infusion (n=20) and 66.7% were not (Table 1).

Table 2 shows the comparison of BP between the good and poor functional outcome groups. A significant difference was found between the groups in terms of diastolic BP at the time of admission to the emergency department, immediately before IV thrombolytic therapy, and at the 15th, 30th, 45th and 60th minutes during the therapy (P=0.025, P=0.047, P=0.039, P=0.004, P=0.005 and P=0.002, respectively). The mean diastolic BP was higher (P=0.01) in the poor functional outcome group (85.92 mmHg) than in the good functional outcome group (71.43 mmHg). Similarly, the mean systolic BP was higher in the poor functional outcome group than in the good functional outcome group (152 mmHg and 136.98 mmHg, respectively), although this difference was not statistically significant (P=0.181) (Table 2).

In Table 3, univariate analysis was performed with age, gender, stroke subtype, obstructed artery, and recanalization variables. Since there was no statistically significant difference in univariate analysis, multivariate analysis was not performed.

Table 1: Comparison of clinical characteristics and risk factors of the study and control groups

Characteristics		Study group n	Study group %	Control group n	Control group %	P-value
Sample size	60	20	33.3	40	66.7	
Gender	Male	9	45.0	18	45.0	1.000
	Female	11	55.0	22	55.0	
HT	Yes	15	75.0	34	85.0	0.481
	No	5	25.0	6	15.0	
DM	Yes	5	25.0	14	35.0	0.560
	No	15	75.0	26	65.0	
Hyperlipidemia	Yes	3	15.0	14	35.0	0.136
	No	17	85.0	26	65.0	
AF	Yes	4	20.0	16	40.0	0.154
	No	16	80.0	24	60.0	
CAD	Yes	4	20.0	11	27.5	0.753
	No	16	80.0	29	72.5	
CHF	Yes	0	0.0	6	15.0	0.165
	No	20	100.0	34	85.0	
Heart valve disease	Yes	1	5.0	2	5.0	1.000
	No	19	95.0	38	95.0	
Atrial thrombus	Yes	0	0.0	0	0.0	-
	No	20	100.0	40	100.0	
Stroke or TIA history	Yes	2	10.0	6	15.0	0.707
	No	18	90.0	34	85.0	
Functional outcome	Good functional outcome (mRS:0-2)	8	40.0	12	30	0.268
	Poor functional outcome (mRS:3-6)	12	60.0	28	70	-
		Mean (SD)		Mean (SD)		P-value
Age, years		62.8 (16.4)		75.1 (10.2)		0.003
Basal NIHSS		12.3 (4.6)		9.3 (5.8)		0.003

HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, CAD: Coronary artery disease, CHF: Congestive heart failure, TIA: Transient ischemic attack, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, SD: Standard deviation

Table 2: Comparison of blood pressures of patients grouped according to functional outcome

	Good functional outcome Mean (SD)	Poor functional outcome Mean (SD)	P-value
Systolic BP at first admission	140.63 (27.18)	155.25 (17.73)	0.181
Diastolic BP at first admission	71.63 (14.37)	86.08 (9.37)	0.025
Systolic BP level just before infusion	137.38 (25.4)	151.08 (15.44)	0.208
Diastolic BP level just before infusion	71.88 (13.28)	84.58 (7.14)	0.047
Systolic BP at 15th minute of infusion	136 (25.86)	152.17 (10.03)	0.057
Diastolic BP at 15th minute of infusion	72.13 (17.85)	85.83 (8.53)	0.039
Systolic BP at the 30th minute of infusion	135.13 (25.01)	152.92 (13.37)	0.082
Diastolic BP at the 30th minute of infusion	69.5 (14.51)	88.17 (7.99)	0.004
Systolic BP at the 45th minute of infusion	138.63 (24.31)	150.5 (11.47)	0.238
Diastolic BP at the 45th minute of infusion	72 (10.06)	85.83 (8.07)	0.005
Systolic BP at the 60th minute of infusion	137.75 (20.25)	153.33 (16.1)	0.115
Diastolic BP at the 60th minute of infusion	71.63 (8.6)	85.17 (7.9)	0.002
Mean systolic BP level during infusion	136.98 (22.57)	152 (11.95)	0.181
Mean diastolic BP level during infusion	71.43 (11.29)	85.92 (6.86)	0.010

BP: Blood pressure, SD: Standard deviation, mRS: modified Rankin Scale

Table 3: Univariate analysis of parameters that may affect functional outcome

		Good functional outcome	Poor functional outcome	P-value
Age, mean (SD)		60.8 (16.8)	64.3 (16.7)	0.792
Gender, n (%)	Male	4 (50.0)	7 (58.3)	0.714
	Female	4 (50.0)	5 (41.7)	
Subtype of Stroke, n (%)				0.652
	Great artery atherosclerosis	2 (25.0)	4 (33.3)	
	Cardioembolic	2 (25.0)	3 (25.0)	
	Cryptogenic	3 (37.5)	5 (41.7)	
	Other	1 (12.5)	0	
	Lacunar syndromes	-	-	
Occluded vessel, n (%)				0.106
	M1 segment of the MCA	0	5 (41.7)	
	M2 segment of the MCA	5 (62.5)	4 (33.3)	
	M3 segment of the MCA	3 (37.5)	3 (25.0)	
Recanalization, n (%)				0.101
	Present	5 (62.5)	2 (16.7)	
	Absent	3 (37.5)	10 (83.3)	

SD: standard deviation, MCA: Middle cerebral artery

There was a significant, positive, and moderate correlation between the 3-month mRS score and diastolic BP at the time of admission to the emergency department and immediately before and during IV thrombolytic therapy (r=0.679, P=0.001; r=0.580, P=0.007; r=0.643, P=0.002, respectively) (Figure 1). Further, there was a significant, positive, and moderate correlation between systolic BP at the time of admission to the emergency department and 3-month mRS score (r=0.471, P=0.036; Figure 1). However, there was no correlation between systolic BP immediately before and during IV thrombolytic therapy and 3-month mRS score (P=0.104 and P=0.107) (Table 4). Figure 2 shows the course of BP during infusion in patients with good and poor functional outcomes.

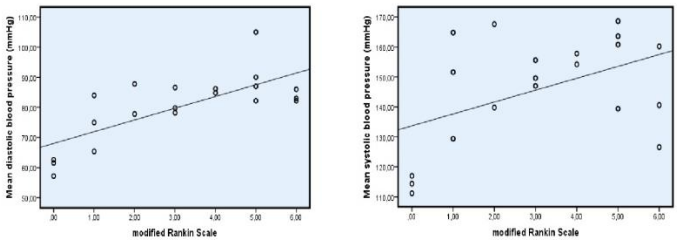

Figure 1: Correlation of mean diastolic blood pressure (r=0.643; P=0.002) and mean systolic blood pressure (r=0.372; P=0.107) during IV thrombolytic infusion with modified Rankin Scale score in the 3rd month

Table 4: Correlation analysis showing the relationship between blood pressure values during infusion and the modified Rankin Scale 3 months after intravenous thrombolytic therapy

		mRS after 3 months
Systolic BP level just before infusion	r	0.374
	P	0.104
Diastolic BP level just before infusion	r	0.580
	P	0.007
Systolic BP at 15th minute of infusion	r	0.431
	P	0.058
Diastolic BP at 15th minute of infusion	r	0.612
	P	0.004
Systolic BP at the 30th minute of infusion	r	0.312
	P	0.180
Diastolic BP at the 30th minute of infusion	r	0.565
	P	0.010
Systolic BP at the 45th minute of infusion	r	0.354
	P	0.126
Diastolic BP at the 45th minute of infusion	r	0.636
	P	0.003
Systolic BP at the 60th minute of infusion	r	0.425
	P	0.062
Diastolic BP at the 60th minute of infusion	r	0.661
	P	0.001
Mean systolic BP level during infusion	r	0.372
	P	0.107
Mean diastolic BP level during infusion	r	0.643
	P	0.002
Systolic BP at first admission	r	0.471
	P	0.036
Diastolic BP at first admission	r	0.679
	P	0.001

Spearman's rho correlation, BP: Blood pressure, mRS: modified Rankin Scale

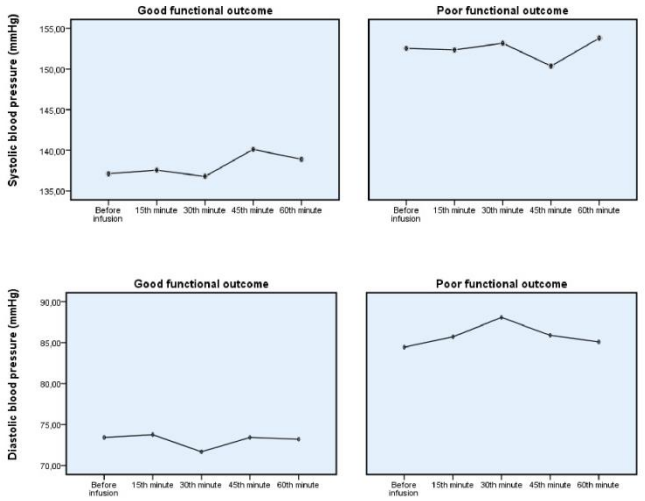

Figure 2: The course of blood pressure during infusion in patients with good and poor functional outcome

Discussion

In this study, a positive correlation was found between diastolic BP of patients undergoing IV thrombolytic therapy at the time of admission to the emergency department and immediately before and during the therapy with the 3-month mRS score and between systolic BP at the time of admission to the emergency department with the 3-month mRS score. In addition, systolic BP immediately before and during IV thrombolytic therapy was found to be insignificantly high in patients with a high mRS score. The insignificance of the difference was attributed to the small sample size. Systolic BP was <140 mmHg and diastolic BP was <75 mmHg in the good functional outcome group.

This study consists of population of patients with large MCA infarction. Patients with large subcortical and cortical infarcts due to large vessel occlusion have a lower efficacy of IV thrombolytic therapy and a higher risk of symptomatic intracerebral hemorrhage (sICH), thereby resulting in poorer therapy outcome [10]. sICH increases mortality rate and is the most feared complication of IV thrombolytic therapy [11,12]. It occurs within the initial 24 h after IV thrombolytic therapy, particularly within the initial 12 h, and tends to be fatal [11]. It is known that high BP increases the risk of sICH [12]. Although the results of the present study demonstrated that maintaining BP within the normal limit during IV thrombolytic therapy is associated with good functional outcome, the optimal BP limits remain to be identified. Nevertheless, maintaining BP within the normal limit or close to the upper limit during IV thrombolytic therapy may prove to be safe in patients with large MCA infarction. AHA/ASA guidelines [3] state that IV thrombolytic therapy can be administered if systolic and diastolic BP are <185 and <110 mmHg, respectively. However, a previous study found that IV thrombolytic therapy resulted in sICH in 25% of their patients with a systolic BP of 165 mmHg [12]. In another study, it was shown that even in cases without sICH, the results obtained at the 3rd month following IV thrombolytic therapy were negatively affected by elevated BP [13]. In their study, Liu et al. [14] found that systolic BP variability within 6 h after IV thrombolytic therapy was positively associated with sICH. In the ENCHANTED study conducted in 2019, although intensive blood pressure reduction was found to be safe due to the decrease in intracranial hemorrhage, it did not lead to better clinical results compared to guideline therapy [15]. This may be different for large vessel infarctions. The present study showed that diastolic BP levels being close to the normal limit during IV thrombolytic therapy, as indicated in clinical practice guidelines [5], results in a good prognosis, whereas higher diastolic BP results in a poor prognosis. Future studies should determine the optimal BP limit that should be maintained during and after IV thrombolytic therapy.

Almost 50% of the patients that undergo IV thrombolytic therapy tend to have good functional outcome at the end of the 3rd month following treatment [16]. In the present study, 40% of the patients had good functional results after the 3rd month following treatment. There may be two reasons for the low rate of patients with good functional outcome, i.e., all patients who underwent IV thrombolytic therapy had large infarcts due to large vessel occlusion and small sample size, which may have affected the results.

In this study, only 33.33% of the patients who were clinically eligible for IV thrombolytic therapy were treated with alteplase therapy after all contraindications were excluded. In other words, 66.67% of the patients who could possibly undergo IV thrombolytic therapy were unable to do so due to various contraindications. In their study, Hess et al. [17] found that the most common reason for not administering IV thrombolytic treatment in rural communities is that the onset-to-needle time exceeds the therapeutic time limit. The California Acute Stroke Pilot Registry study also found that the most common reason that prevented the administration of IV thrombolytic therapy was pre-hospital delay [18]. A low level of awareness about stroke and IV thrombolytic therapy in the general population is thought to play a significant role in this delay [19]. The number of patients who can benefit from IV thrombolytic therapy can be increased through efforts aimed at increasing public awareness about stroke (including the effective use of media) and by government health policies, raising awareness among physicians, and training of first aid and emergency unit personnel.

Limitations

Although we believe that this study will make an important contribution to the existing literature, there are still certain limitations to this study. The most important limitation is the small sample size. Another limitation is its retrospective nature.

Conclusion

It was concluded that there is a possible relationship between diastolic BP level during IV thrombolytic therapy and functional outcomes in patients with large MCA infarction. Further studies are needed to determine the optimal BP limits during IV thrombolytic therapy in patients with AIS.

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