HOW DOES THE USE OF ANTIPLATELET AND ANTICOAGULANTS AFFECT THE SUCCESS OF MECHANICAL THROMBECTOMY IN ACUTE ISCHEMIC STROKE CASES?

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Background and purpose – In this study, we wanted to investigate the effect of antiplatelet and anticoagulant use on the success of mechanical thrombectomy in acute ischemic stroke cases.
Methods – 174 patients who were brought to the Stroke Center of Gaziantep University Şahinbey Research and Practice Hospital between January 2018 and February 2019 due to acute ischemic stroke and who underwent mechanical thrombectomy were retrospectively analyzed. The demographic characteristics, antiplatelet/anticoagulant use before the stroke and mTICI (modified-Thrombolysis-In-Cerebral-Infarction) scores used for reperfusion in mechanical thrombectomy were evaluated. The findings were analyzed statistically ($p<0.05$).
Results – The mean age was 63.3 ± 13.5 in 174 patients who underwent mechanical thrombectomy. 23/174 (13.2%) patients were using anticoagulant therapy (warfarin-OAC or new generation oral anticoagulant-NOAC) and 28/174 (16.1%) were using antiplatelet therapy. A history of atrial fibrillation (AF) was significantly higher in patients receiving anticoagulant therapy before acute ischemic stroke ($p=0.001$). Patients with a history of hyper tension (HT), diabetes mellitus (DM) and coronary artery disease (CAD) before acute ischemic stroke were receiving antiplatelet therapy in higher rates (respectively; $p=0.003$, $p=0.037$, $p=0.005$). Successful recanalization (mTICI ≥

HOGYAN BEFOLYÁSOLJA A THROMBOCYTA-AGGREGÁCIÓ-GÁTLÓK ÉS AZ ANTIKOAGULÁNSOK HASZNÁLATA A MECHANIKUS THROMBECTOMIA SIKERESSÉGÉT AKUT ISCHAEMIÁS STROKE ESETÉN?

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Háttér és cél – A tanulmány célja annak megállapítása volt, hogy hogyan befolyásolja az akut ischaemiás stroke bekövetkezte előtt alkalmazott thrombocytaaggregáció-gátló és antikoaguláns terápia a mechanikus thrombectomia sikerességét.
Módszerek – A Gaziantep Egyetem Stroke Központjában 2018 januárja és 2019 februárja között akut ischaemiás stroke miatt mechanikus thrombectomiával kezelt 174 beteg adatait elemeztük retrospektív módon. Értékeltük a betegek demográfiai sajátosságait, a stroke bekövetkezte előtt alkalmazott thrombocytaaggregáció-gátló és antikoaguláns terápiájukat és a mechanikus thrombectomia sikerességét jelző, azaz a reperfúzió mérése érdekében rögzített módosított TICI- (Thrombolysis-In-Cerebral-Infarction) pontszámukat. Az eredményeket $p < 0,05$-os statisztikai szignifikanciaszinttel elemeztük.
Eredmények – A mechanikus thrombectomián áteső 174 beteg átlagos életkora 63,3 ± 13,5 volt. 23/174 (13,2%) beteg részesült a stroke-ot megelőzően antikoaguláns terápiában (warfarin/OAC vagy új generációs orális antikoaguláns/NOAC) és 28/174 (16,1%) részesült thrombocytaaggregáció-gátló kezelésben. Szignifikánsan ($p = 0,001$) magasabb volt azoknak az akut ischaemiás stroke-ot megelőzően antikoaguláns terápiában részesült betegeknek a száma, akik kórtörténetében pitvarfibrilláció szerepelt. Azok a betegek, akik kórtörténetében az akut

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2b) was higher in patients with a history of anticoagulant use and who underwent mechanical thrombectomy (p=0.025).
Conclusion – Our study showed that the use of antiplatelet or anticoagulants before mechanical thrombectomy may have an indirect positive effect on the success of the procedure.

Keywords: *ischemic stroke, antiplatelet therapy, anticoagulant therapy, mechanical thrombectomy*

ischaemiás stroke-ot megelőzően hypertonia (HT), diabetes mellitus (DM) vagy koszorúér-betegség (CAD) szerepelt, nagyobb arányban részesültek thrombocytaaggregáció-gátló kezelésben (p = 0,003; p = 0,037; p = 0,005). A sikeres rekanalizáció (mTICI ≥ 2b) aránya nagyobb volt abban a mechanikus thrombectomiában részesült betegcsoportban, amelynek tagjai az akut ischaemiás stroke-ot megelőzően antikoaguláns terápiát kaptak (p = 0,025).
Következtetés – Vizsgálatunk eredménye azt mutatja, hogy a mechanikus thrombectomia előtti thrombocyta-aggregáció-gátló és antikoaguláns terápia indirekt pozitív hatással lehet a mechanikus thrombectomia sikerességére.

Kulcsszavak: *ischaemiás stroke, thrombocytaaggregáció-gátló kezelés, antikoaguláns terápia, mechanikus thrombectomia*

Antiplatelets such as acetylsalicylic acid, clopidogrel, and warfarin-like anticoagulants are common agents in the primary and secondary treatment of cardiovascular, cerebrovascular diseases and embolic events. While anticoagulants are particularly preferred in cardioembolic stroke and transient ischemic attack, there is no convincing evidence that any of the available antiplatelets is superior for a particular stroke subtype. To maximize the effects of these agents, it is recommended to use them combined, start treatment as early as (within the first 24 hours of stroke) possible and continue for a long time. Antiaggregant therapy is often continued as monotherapy in stroke patients, however dual antiaggregant therapy is recommended for 1-3 months in some cases[1, 2]. As it is known, mechanical thrombectomy (MT) is the recommended – class I, level of evidence A – life-saving method in patients with acute ischemic stroke and who are suitable for endovascular treatment[3]. In current studies, mTICI (modified-Thrombolysis-In-Cerebral-Infarction) grade 2b and above is considered as a technical success for reperfusion in MT, while it is predicted to be TICI 3 for clinical success[4, 5]. The structure of the clot has an important place in the success of the MT procedure as well as the duration and localization of the arterial occlusion[6]. In this study, we wanted to investigate the effect of antiplatelet and anticoagulant use before the stroke on MT treatment and discuss the clinical outcomes in patients with acute ischemic stroke.

Materials and methods

The study is a single center retrospective trial of 174 ischemic stroke patients who underwent mechanical thrombectomy between January 2018 and February 2019. Patients' demographic, clinical and radiological data were collected and analysed. The trial site is the Stroke Center of the Gaziantep University, Turkey. The study was approved by local ethical comittee, dated 25.12.2019 and 2019/480.

The demographic and clinical features of the patients, NIHSS (National Institues of Health Stroke Scale) scores, ASPECT (Alberta Stroke Programe Early Computed Tomography Score) scores, occlusion site, intravenous (IV) recombinant tissue plasminogen activator (r-tPA) before the procedure, antiplatelet / anticoagulant usage in the history, symptom puncture / recanalization times (min), intra-arterial (IA) r-tPA during the procedure, total intracranial procedure numbers, technique used (ADAPT – aspiration technique – or stent retriever technique), mTICI for reperfusion scores, biochemistry-hemogram values, presence of concomitant chronic disease [diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), previous stroke history, atrial fibrillation (AF) and obesity] were collected. The mRS (modified Rankin Scale) scores and mortality development in the month were analyzed.

STATISTICAL ANALYSIS

IBM SPSS Statistics 22.0 program was used for statistical analysis. While evaluating the study data, Mann-Whitney U test was used for descriptive statistical methods (mean, standard deviation, median, frequency, 25-75 percentile, percent), and Chi-square test was used to compare the grouped data. The results were evaluated in the 95% confidence interval and the significance level was $p < 0.05$.

Results

The mean age of the 174 patients who underwent mechanical thrombectomy was 63.3 ± 13.5 years. NIHSS median 16 (14-16) (percentile 25-75) and brain computerized tomography (CT) ASPECT score median at the time of first arrival were 9 (8-10) (percentile 25-75). IV r-tPA was applied to 24 (13.8%) patients. 23 (13.2%) patients were using anticoagulant therapy (warfarin-OAC or new generation oral anticoagulant-NOAC) and 28 (16.1%) were using antiplatelet therapy before the stroke. There were a total of 123 (70.7%) patients who were using neither antiaggregant nor anticoagulant drugs, and there was no patient using both.

A history of AF was found to be significantly higher in patients receiving anticoagulant therapy before acute ischemic stroke (p = 0.001). Prior to acute ischemic stroke, patients with a history of HT, DM and CAD were receiving antiplatelet therapy in higher rates (respectively; p = 0.003, p = 0.037, p = 0.005). Administration of IA r-tPA before the mechanical thrombectomy procedure was significantly lower in patients receiving anticoagulant therapy (p = 0.017) **(Table 1)**. In patients receiving antiplatelet therapy before acute ischemic stroke, the symptom-femoral puncture time was long, and the symptom-recanalization time was found to be significantly longer (p = 0.010, p = 0.016) **(Table 2)**. Successful recanalization (mTICI ≥ 2b) was higher in patients with a history of anticoagulant use and mechanical thrombectomy (p = 0.025) **(Table 1** and **Table 3)**. Moreover, as indicated in **Table 1**, the rate of successful recanalization in the first 45 minutes was higher in patients who received anticoagulant therapy and had a stroke (p = 0.025).

During the procedure 158 (90.8%) patients were given a retractable stent (stent retriever) and after the procedure 154 (88.5%) patients had mTICI 2b and above grade recanalization. At the end of the 3rd month, 87 (50%) had good clinical outcomes between 0 and 3; 65 patients (35.1%) deceased.

Discussion

It would be better to describe ischemic stroke as a complex syndrome with multiple etiologies and heterogeneous mechanisms, rather than as a simple disease. Approximately 1/3 of the patients who have an ischemic stroke experience an ischemic event again, especially in the first few months[1].

Table 1. *Comparison of stroke risk factors and clinical data in patients receiving anticoagulant and antiplatelet therapy before stroke*

Demographic data and clinical results	Anticoagulant theraphy		p	Antiplatelet theraphy		p
	No n (%)	Yes n (%)		No n (%)	Yes n (%)	
Gender (female)	69 (82.1)	15 (17.9)	0.081	72 (85.7)	12 (14.3)	0.531
Stroke side (right)	62 (80.5)	15 (19.5)	0.165	67 (87)	10 (13)	0.324
IV-r-tPA	22 (91.7)	2 (8.3)	0.447	19 (79.2)	5 (20.8)	0.496
mTICI 2b-3 and above recanalization	135 (87.7)	19 (12.3)	0.341	129 (83.8)	25 (16.2)	0.888
Successful recanalization with the first pass	44 (84.6)	8 (15.4)	0.582	42 (80.8)	10 (19.2)	0.462
Successful recanalization in the first 45 minutes	28 (75.7)	9 (24.3)	*0.025*	34 (91.9)	3 (8.1)	0.136
IA lytic therapy	104 (91.2)	10 (8.8)	*0.017*	92 (80.7)	22 (19.3)	0.113
After endovascular treatment						
CT bleeding	63 (87.5)	9 (12.5)	0.814	60 (83.3)	12 (16.7)	0.862
mRS (0-3) in the third month	76 (87.4)	11 (12.6)	0.823	77 (88.5)	10 (11.5)	0.099
Mortality in the third month	56 (91.8)	5 (8.2)	0.151	48 (78.7)	13 (21.3)	0.169
Atrial fibrillation	37 (64.9)	20 (35.1)	*0.001*	49 (86)	8 (14)	0.606
Hypertension	84 (85.7)	14 (14.3)	0.637	75 (76.5)	23 (23.5)	*0.003*
Obesity	12 (80)	3 (20)	0.417	14 (93.3)	1 (6.7)	0.299
Diabetes	55 (87.3)	8 (12.7)	0.879	48 (76.2)	15 (23.8)	*0.037*
Coronary artery disease	31 (79.5)	8 (20.5)	0.127	27 (69.2)	12 (30.8)	*0.005*
Previous stroke	11 (73.3)	4 (26.7)	0.108	12 (80)	3 (20)	0.667

Chi-squared test.

IV-r-tPA: intravenous recombinant tissue plasminogen activator, mTICI: modified-thrombolysis-in-cerebral-infarction, IA: intra-arterial, CT: computerized tomography, mRS: modified Rankin Scale

Table 2. *Comparison of endovascular treatment procedure and blood tests between the patients receiving anticoagulant and antiplatelet therapy before stroke*

Endovascular treatment data and blood test results	Anticoagulant theraphy		p	Antiplatelet theraphy		p
	No Median (25-75)	Yes Median (25-75)		No Median (25-75)	Yes Median (25-75)	
Age	66 (56-74)	68 (53-75)	0.706	67 (56-75)	65 (56-71)	0.572
Application NIHSS	16 (14-20)	18 (14-21)	0.667	16 (14-20)	18 (14-20)	0.707
CT ASPECT	9 (8-10)	9 (8-10)	0.512	9 (8-10)	9 (8-10)	0.689
Symptom femoral puncture (min)	200 (120-260)	180 (120-240)	0.316	200 (120-260)	240 (182-300)	*0.010*
Symptom recanalization (min)	270 (200-340)	255 (180-310)	0.150	262 (195-320)	317 (237-387)	*0.016*
Total intracranial procedure	3 (2-5)	3 (2-4)	0.503	3 (2-4)	2 (1-4)	0.094
Third month mRS	3 (2-6)	4 (2-5)	0.193	3 (2-6)	5.5 (2-6)	0.533
Glucose	142 (117-200)	130 (111-165)	0.198	136 (113-178)	156 (119-211)	0.139
Leukocyte	10380 (8350-12800)	9100 (7810-12890)	0.283	10185 (8390-12810)	10490 (8010-12480)	0.881
Platelets	258 (216-308)	252 (190-348)	0.855	258 (216-312)	269 (223-302)	0.725
Hemoglobin	13.2 (11.9-14.4)	12.8 (11.5-13.9)	0.426	13 (11.9-14.4)	13.5 (12.1-14.4)	0.465
RDW	14.2 (13.4-15.3)	14.3 (13.6-16.2)	0.608	14.2 (13.4-15.3)	14.3 (13.6-15.4)	0.532

Mann-Whitney U test.
NIHSS: National Institutes of Health Stroke Scale, CT: computerized tomography, mRS: modified Rankin Scale, RDW: red cell distribution width

Understanding the complex pathophysiology of ischemic stroke is possible by understanding the underlying etiological causes. For this purpose, the TOAST (The Trial of Org 10172 in Acute Stroke Treatment) classification system has been developed to categorize the ischemic stroke subtypes and thus select the correct management guide[7].

To date, antiplatelet agents that have been approved by FDA (Food and Drug Administration) in secondary protection include acetylsalicylic acid, clopidogrel and dipyridamole. These inhibit different regions of platelet activation pathways[1, 8]. Warfarin is the most used agent among anticoagulants. Low-molecular-weight heparin (LMWH) or new oral anticoagulants (NOAC) are alternatives if starting warfarin is contraindicated, if an unwanted side effect has occurred, resistance has improved, or the patient cannot be followed closely to reach high dose treatment options[9, 10]. In our study, only 28 (16.1%) patients were using antiplatelet therapy for different reasons before MT. The number of patients receiving anticoagulant therapy before the procedure was 23 (13.2%). However, the average age of our patients was high (63.3 ± 13.5). In the group of patients with concomitant chronic diseases there was a history of stroke in 15 (9%), HT in 98 (56%), DM in 63 (36%), CAD in 39 (22%) and AF in 57 (32.8%). Among these risk factors, AF is the most common rhythm disorder and its prevalence increases with age. One of the most important goals in the treatment of these patients is to prevent thromboembolism. It is imperative to follow the current guidelines to achieve this goal. In recent years, a scoring system has been developed in AF patients and a risk calculation table has been created[11]. Anticoagulant or antiplatelet therapy can be recommended in patients with a CHA2DS2-VASc score of 1, while anticoagulation is essential in patients with a score of 2. In our study, it was seen that warfarin was not used, and even antiplatelet therapy was not used in an important group of patients who should definitely use warfarin. In the WARFARIN-TR study conducted by *Kılıç* et al., the INR (International Normalized Ratio) value was found to be the lowest in the Southeastern Anatolia region[12]. Our study consisted people from the population of Gaziantep, which is the most dense province of Southeastern Anatolia region, and the

Table 3. *Comparison of recanalization success in the first 45 minutes in patients receiving anticoagulant therapy before mechanical thrombectomy procedure*

In the first 45 minutes recanalization	Anticoagulant theraphy		p
	No n (%)	Yes n (%)	
Unsuccessful	123 (89.8)	14 (10.2)	*0.025*
Successful	28 (75.7)	9 (24.3)	

Chi-squared test

surrounding cities. In addition, according to the findings of our study, there was another patient group who had an acute ischemic stroke despite receiving anticoagulants and antiplatelet therapy. In this group of patients, the cause of stroke may be insufficient drug therapy or resistance to drugs. Successful recanalization rate was higher in the first 45 minutes after acute ischemic stroke in this group, where MT was administered and anticoagulants were received **(Table 1** and **Table 3)**. This may lead us to conclude that the clot is unstable or the clot composition is different in these patients receiving anticoagulants due to AF (aware of the red and white thrombus). It can be said that the difference in thrombus structure may have an effect on successful recanalization in the first 45 minutes, since AF is frequent in patients receiving anticoagulant therapy[13]. There was no such a significant difference between the groups that received antiplatelet or did not. This can be explained by the fact that there is a lower treatment compliance to antiplatelet therapy compared to anticoagulant use. Studies have shown that despite antiplatelet therapy, a significant number of patients have recurrent ischemic attacks called aspirin or clopidogrel treatment failure. *Vadász* et al. reported that they did not reach a sufficient level of efficacy in platelet activation in approximately 30% of cases treated with aspirin and in 20% of cases treated with clopidogrel[14]. In our study, 24 (13.8%) patients were given IV r-tPA before MT. Studies have shown that IV r-tPA use before mechanical thrombectomy provides successful reperfusion in one of ten cases without the need for endovascular treatment; tandem occlusions are the least responsive[15]. In our study, there was no statistical difference in terms of transaction success between those who got IV r-tPA before MT or who did not. Due to the low number of patients who received IV r-TPA in our study, we did not perform statistical analysis for this group. However, the use of IV r-TPA alone cannot provide successful recanalization for tandem occlusions with high clot load, as stated in the literature[16]. In our study, 10 patients (8.8%) who were using anticoagulants and 22 (19.3%) who received antiplatelet therapy received IA r-tPA therapy during mechanical thrombectomy. Administration of IA r-tPA before the mechanical thrombectomy procedure was significantly lower in patients receiving anticoagulant therapy (p = 0.017) **(Table 1)**. Again, according to current data, r-tPA dose should be kept low due to the risk of bleeding in these patients and attention should be paid to keep the INR level between 1.7-2[17]. In our study, it was observed that the patients who previously used anticoagulants, received less IA r-tPA dose during MT. This may be due to the fact that the IA r-tPA dose is kept low or not administered due to the risk of bleeding. However, in a study by *Berkhemer* et al., IA r-tPA treatment was found to be effective and safe in patients with acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation in the first 6 hours after stroke[18].

Experimental studies have shown that the effectiveness of advanced thrombectomy techniques may depend on thrombus morphology. *Madjidyar* et al. claimed that determining the correct technique for the correct clot could improve MT results[6]. It is difficult to draw such a conclusion in our cases, since different operators and different techniques were used. The most important factor affecting thrombus morphology is time. *Yang* et al. showed in their experimental study on the time-related organization of thrombus that it was more organized as time passed[19]. In another study, *Ramaiola* et al. showed that the thrombus aspirated within 6 hours after ischemia is richer in fibrin than those aspirated within 3 hours[20]. Other factor affecting thrombus formation is whether the thrombus is arterial or venous in origin. Thrombi of arterial origin consist of high pressure resistant, platelet- and fibrin-rich structures (white thrombus). The thrombi originating from the venous system and the cardiac atrium have low pressure-resistant structures (red thrombus) consisting of mostly erythrocytes[21].

It has been thought that long-term use of anticoagulants or antiplatelet therapy may affect the thrombus structure of patients with acute ischemic stroke for the underlying etiology. Today we know many factors that affect the success of the MT procedure performed in these cases. We must search after the answers to these questions: How much do the anticoagulant and antiplatelet medications affect the thrombus structure? or Is there any resistance to these medications?

Our study is a retrospective study based on file records. The limitations of our study are that differ-

ent operators performed the mechanical thrombectomy procedure, different materials were used and different techniques were chosen, that is to say the absence of a standardization. However, our study is important in terms of guiding prospective studies.

As a result, we found that the use of anticoagulants or antiplatelet therapy prior to MT may have an indirect positive effect on the success of the procedure. Further experimental or randomized controlled studies are needed in this regard.

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