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Evaluation of Acute Ischemic Stroke Patients Treated with Intravenous Thrombolysis; Experiences of a Stroke Center

İntravenöz Trombolitik Tedavi Verilen Akut İskemik İnmeli Hastaların Değerlendirilmesi; Bir İnme Merkezinin Deneyimleri

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Abstract

INTRODUCTION: Intravenous thrombolytic (iv-tPA) treatment is a recommended treatment in acute ischemic stroke (AIS). We aimed to evaluate the effectiveness and side effects of this treatment on our patients.
METHODS: We retrospectively evaluated the datas of patients with AIS treated with 0,9 mg/kg iv-tPA between 2018-2020.
RESULTS: Forty-nine patients were treated with iv-tPA between 2018 and 2020. NIHSS scores at 24th hour were found significantly decreased compared with at onset(8,3±4,1 at onset, 4,9±5,1 at 24th hour, p=0,000). Thirty-eight (%77,6) patients had good clinical outcome. Intracerebral hemorrhage (ICH) was spotted in 3 (6,1%) patients. Systolic blood pressure (ICH group: 163±59 mmHg, non-ICH group: 141±25 mmHg p=0,014), serum glucose level(ICH group: 173±117 mg/dl, non-ICH group: 124±45mg/dl, p=0,007) and mean door-needle time (ICH group: 125±9 min., non-ICH group: 137±54 min. p=0,029) were found significantly increased in patients with ICH. Total 4 (8,2%) patients died after iv-tPAtreatment.
DISCUSSION AND CONCLUSION: Our study showed that iv-tPA improves the clinical findings of AIS. Additinally high serume glucose level and systolic blood pressure may increase the risk of ICH.

Keywords: ischemic stroke, intravenous thrombolytic, alteplase

Öz

GİRİŞ ve AMAÇ: İntravenöz trombolitik (iv-tPA) tedavi, akut iskemik inmeli hastaların tedavisinde önerilen bir yöntemdir. Bu çalışmadaki amacımız iv-tPA'nın hastalarımızdaki etkinliğini ve yan etkilerini incelemektir.
YÖNTEM ve GEREÇLER: Merkezimizde 2018-2020 yılları arasında 0,9mg/kg dozunda iv-tPA alan hastların verileri retrospektif olarak incelendi.
BULGULAR: Merkezimizde 2018-2020 yılları arasında 49 hastanın iv-tPA ile tedavi edildiği saptandı. Iv-tPA ile tedavi edilen hastaların 24. saat NIHSS skorlarının tedavi öncesi NIHSS skorlarına göre belirgin düşük olduğu izlendi(tedavi öncesi 8,3±4,1; 24. saat 4,9±5,1, p=0,000). Hastaların 38'inde (%77,6) iyi klinik prognozun olduğu izendi. Üç (%6,1) hastada intraserebral kanama olduğu izlendi. İntraserebral kanama olan hastalarda sistolik kan basıncının(kanama olanlar: 163±59 mmHg, kanama olmayanlar: 141±25 mmHg p=0,014), serum glukoz düzeyinin(kanama olanlar: 173±117 mg/dl, kanama olmayanlar: 124±45mg/dl, p=0,007) ve kapı-iğne sürelerinin(kanama olanlar: 125±9 dk, kanama olmayanlar: 137±54 dk p=0,029) daha yüksek olduğu izlendi.
TARTIŞMA ve SONUÇ: Çalışmamız iv-tPA'nın akut iskemik inmeli hastaların klinik bulgularını düzelttiğini gösterdi. Ayrıca yüksek serum glukoz düzeyi ve sistolik kan basıncının da intraserebral kanama riskini artırdığı izlendi.

Anahtar Kelimeler: iskemik inme, intravenöz trombolitik, alteplaz

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INTRODUCTION

Intravenous thrombolytic (iv-tPA) treatment is a recommended treatment in acute ischemic stroke (AIS). In 1995, National Institute of Neurological Disorders and Stroke study group reported that patients with acute ischemic stroke who were treated with alteplase 0,9mg/kg within 3 hours after onset of symptoms had better disability rates(1). ECASS III study showed that iv-tPA had benefit on patients treated 3-4,5 hours after onset of stroke sympthoms(2). In American Hearth Association/American Stroke Association (AHA/ASA) guidelines, iv-TPA was recommended for patients who may be treated in 4,5 hours(3). Usage of iv-tPA in treatment of AIS spreads in our country. In this study, we evaluated the patients with acute ischemic stroke who were treated with iv-tPA

MATHERIAL AND METHODS

We retrospectively evaluted the datas of patients with AIS in Kocaeli Derince Training and Research Hospital between 2018-2020. This study was approved by Kocaeli Derince Training and Research Hospital Ethic Committee. Datas were collected from hospital records. Patients or their relatives were phoned for missing datas.

Iv-tPA treatment was applied patients who didn't have any contraindication according to guideline of AHA/ASA (3). Iv-tPA was given as dose of 0,9mg/kg (maximum 90 mg) over 60 minutes with initial 10% given as bolus over 1 minute. All patients with acute ischemic stroke who were treated with iv-tPA didn't have large vessel occlusion (LVO) (internal carotid artery or M1 segment of middle cerebral artery) in computarized thomography (CT) angiograhy were included to our study. Patients with large vessel occlusions were excluded, because they were treated with endovascular techniques.

Demographic datas, medical history (diseases, drugs,etc), laboratory findings (blood cell counts, glucose, kidney function tests, liver function tests, lipid profile, International Normalized Ratio (INR), hemoglobin A1c, etc), systolic and diastolic blood pressures at admission, sympthom-needle time, sympthom-door time, door-needle time, Alberta Stroke Program Early Computed Tomography Score (ASPECT)(4) on non-contrast brain CT at admission, National Institutes of Health Stroke Scale (NIHSS) score at admission and 24th hour, brain CT findings at 24th hour and modified Rankin score (mRS) at 90th day were collected. Sympthom-needle time was defined as time from onset of sympthoms to bolus injection of iv-tPA. Sympthom-door time was defined as time from onset of sympthoms to arrival to hospital. Door-needle time was defined as time from arrival to hospital to bolus injection of iv-tPA. Intracerebral hematoma (ICH) types on brain CT at 24th hour were defined according to European Collaborative Acute Stroke Study (ECASS) classification (5). Subtypes of ischemic stroke were defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification(6).

Statistical analyzes were made with SPSS 15.0. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean (SD) or median (interquartilerange [IQR]) for non-normal distribution. Kolmogorov-Smirnov test was used for assessing the normality of distribution. We used Mann-Whitney U, paired T and independent T-tests for continuous data and χ^2 for binary and categorical data. All p values <0,05 were considered significant.

RESULTS

We achieved datas of 49 patients treated with iv-tPA between July 2018 and December 2020.Twenty-eight (57,1%) patients were male. Mean age of patients was found as 67,4±12,3 years (Male:68,5±12,5; female:66±12,2; p=0,985). Smoking was found high in males (p=0,04; OR:0,152, 95% CI 0,04-0,574). Hypertension (HT) was found increased in females (p=0,014; OR:11,111, 95%CI 1,292-95578). Other risk factors were found similar between male and female patients. Sympthom-needle, symptom-door and door-needle times were found similar between males and females. Mean ASPECT score was found 9,6±0,7 points (Median:10, males: 9,7±0,6, females: 9,6±0,7, p=0,573). In laboratory findings, mean platelet count was increased and mean creatine level was decreased in female patients. Twenty-two (44,9%) patients had usage of antiaggregants before stroke (17[34,7%] patients acetylsalicylic acid (ASA), 2[4,1%] patients klopidogrel, 3[6,1%] patients ASA+klopidogrel. Atherosclerotic ischemic stroke was found high in male patients (p=0,015). Demographic, laboratory and clinical datas were shown in Table 1.

Mean NIHSS score at onset was 8,3±4,1 points (Males: 9,1±4,6; females:7,1±3,2, p=0,131). Mean NIHSS score 24th hour was found as 4,9±5,1 points (males: 5,6±6,1, females:3,9±3,1, p=0,575). Mean NIHSS score of all patients decreased significantly at 24th hour(p=0,000, p=0,019 for males, p=0,007 for females). Changes in NIHSS scores were shown in Table 2.

ICH was seen in 3 (6,1%) patients on brain CT performed at 24th hour. One patient had petechial hemorrhage type 2 and 2 patients had parenchimal hematoma type 2. We found decreased sympthom-door time (ICH group: 125±9 min., non-ICH group: 137±54 min. p=0,029) and increased door-needle time (ICH group: 73±37 min., non-ICH group: 37±9 min. p=0,009) in patients with ICH. Systolic BP was found high in patients with ICH(ICH group: 163±59 mmHg, non-ICH group: 141±25 mmHg p=0,014). In laboratory findings, only serum glucose levels were found increased in ICH group (ICH group: 173±117 mg/dl, non-ICH group: 124±45mg/dl, p=0,007).

Good clinical outcomes were seen in 38 (77,6%) of 49 patients. Distribution of mRS was shown in Table 3. Mean ASPECT score was found increased (p=0,037), and NIHSS score at 24th hour was found decreased (p=0,001) in patients with good clinical outcome. In laboratory findings, thyroxine (T4) levels were found high in patients with good clinical outcome(p=0,029). Ischemic stroke in medical history was found high in patients with poor clinical outcome (p=0,007; OR:21,143, 95%CI 2,046-218,497). Datas of patients with good and bad clinical outcome were shown in Table 4. Four (8,2%) patients died. Two (4,1%) patients died because of ICH, 1 (2%) patient died because of aspiration pneumonia and 1 patient died because of COVID-19 infection.

Table 1: Demographic, clinical, radiological and laboratory findings of male and female patients

	Overall (%)	Male (%)	Female (%)	p
Patients	49	28(57,1)	21(42,9)	
Age	67,4±12,3	68,5±12,5	66±12,2	0,985
Hypertension	37(77,6)	18(64,3)	20(95,2)	0,014
Diabetes Mellitus	10(20,4)	4(14,3)	6(28,6)	0,291
Smoking	21(42,9)	17(60,7)	4(19)	0,004
Coronary Artey Disease	8(16,3)	6(21.4)	2(9,5)	0,438
Hyperlipidemia	6(12,2)	3(10,7)	3(14,3)	1,000
Stroke History	5(10,2)	5(17,9)	0(0)	0,062
Atrial Fibrillation	14(28,6)	7(25)	7(33,3)	0,542
Hearth Failure	3(6,1)	2(7,1)	1(4,8)	1,000
Sympthom-needle time (min)	178±49	181±46	173±53	0,316
Sympthom-door time (min)	135±51	141±45	128±59	0,143
Door-needle time(min)	39±14	40±16	38±12	0,456
ASPECT	9,6±0,7	9,7±0,6	9,6±0,7	0,573
NIHSS at onset	8,2±4,1	9,1±4,6	7,1±3,2	0,131
NIHSS at 24th hour	4,9±5,1	5,6±6,1	3,9±3,1	0,575
Cardioembolism	14(28,6)	7(25)	7(33)	0,542
Atherosclerotic	7(14,3)	7(25)	0(0)	0,015
Lacunary infarction	10(20,4)	5(17,9)	5(23,8)	0,726
Undefined cause	18(36,7)	9(32,1)	9(42,9)	0,318
WBC(/mm^3)	8500±4109	9085±5050	7719±2228	0,234
Neutrophile %	62,5±14,7	61,8±16,8	63,3±11,6	0,402
Hemoglobin(gr/dl)	12,6±2,3	13,2±2,5	11,8±1,8	0,353
MCV(fl)	84,7±13,8	82,6±17	87,5±7,1	0,466
Platelet(/mm$_3$)	242408±74653	225642±56179	264761±90534	0,029
MPV(fl)	8,99±0,9	9,1±0,95	8,84±0,83	0,647
Glucose (mg/dl)	127±51	129±55	123±47	0,952
Urea (mg/dl)	38,2±18,6	36,3±11,9	40,8±25,1	0,505
Creatine(mg/dl)	0,92±0,38	0,93±0,23	0,90±0,53	0,019
AST(U/L)	39,1±106,5	27,3±20,8	54,9±161,8	0,169
ALT(U/L)	28,6±73,2	18,4±10,3	42,2±111,2	0,460
GGT(U/L)	32,4±40,1	22,6±10,2	45,3±58,3	0,123
INR	1,07±0,12	1,09±0,09	1,06±0,15	0,294
CRP(mg/l)	13,5±14,9	12,6±13,6	14,8±16,7	0,418
Triglyceride(mg/dl)	133,5±61,8	126,4±55,6	143,3±70	0,409
Total Kolesterol(mg/dl)	189,1±42,8	183,6±43,1	196,8±42,4	0,904
HDL(mg/dl)	42,3±13,3	41,2±14,1	43,7±12,4	0,827
LDL(mg/dl)	121,3±35,9	118,9±38,8	124,4±32,1	0,364
TSH(µU/ml)	2,78±6,23	3,11±7,87	2,26±1,92	0,250
T3(pg/ml)	2,57±0,46	2,62±0,52	2,5±0,36	0,184
T4(ng/ml)	1,22±0,22	1,18±0,19	1,27±0,25	0,234
HbA1c(%)	6,25±1,38	6,5±1,73	5,91±0,53	0,256
Systolic BP(mmHg)	143±29	147±27	135±30	0,387
Diastolic BP(mmHg)	81±15	83±16	77±14	0,236
Antiaggregant	22(44,9)	13(46,4)	9(42,9)	0,865
Warfarin	3(6,1)	2(7,1)	1(4,8)	1,000
ICH	3(6,1)	3(10,7)	0(0)	0,250
Good Clinical Outcome	38(77,6)	20(71,4)	18(85,7)	0,311
Mortality	4(8,2)	4(14,3)	0(0)	0,125

Table 2: NIHSS Score Changes Between at Onset and at 24th Hours

	NIHSS at onset	NIHSS at 24th hour	p
Overall	8,2±4,1	4,9±5,1	0,000
Male	9,1±4,6	5,6±6,1	0,019
Female	7,1±3,2	3,9±3,1	0,007

Table 3: Distribution of mRS at 90th day

mRS	n(%)
0	10(20,4)
1	18(36,7)
2	10(20,4)
3	6(12,2)
4	1(2)
5	0(0)
6	4(8,2)

DISCUSSION

In this study, we evaluated the datas of ischemic stroke patients treated with iv-tPA who didn't have LVO. We found that clinical findings of patients significantly recovered in 24 hours after treatment. Additinally 77,6% of patients had functional independence at 90th day, and 8,2% of patients died due to ICH or infections. In a study, NINDS reported that 60% of patients had mRS≤ 3 points(1). In SITS-MOST study, functional independence (mRS≤2) rate of patients was found as 54,8%(7). In ECASS III study, favourable outcome was seen in 52,4% of patients treated with iv-TPA in 3-4,5 hours(2). Good clinical outcome was found as 62,7% in SITS-ISTR study(8).In a recent study, good clinical outcome at 3rd month was seen in 65% of patients in Turkey(9). Our good clinical outcome rate was found high from other trials. InAHA/ASAguideline published in 2015, endovascular treatment was considered in patients with LVO(10). In our center, patients with LVO are treated with mechanical thrombectomy. So patients with LVO were excluded from our study. But in these studies were designed before 2015, and patients with LVO were treated with only iv-tPA. But, recanalization rate was found as in 5.9 % patients with distal ICA occlusion after iv-tPA alone in a trial(11). Exclusion of patients with LVO might increase the rate of good clinical outcome in our study.

Early admission of iv-tPAincreases the efficacy of this treatment. Sympthom-door time was found 157 minutes in SITS-ISTR trial(8). Our findings were similar to this trial. But mean symthom-door time was found low in two recent studies performed in Turkey(9, 12). Our hospital is only center treating AIS patients with iv-tPA and endovascular techniques in our region. Most of our patients came from other hospitals. Neurologists in these hospitals don't want to treat AIS patients with iv-tPA due to not having experience it, and they send these patients to our hospital. This situation increased the sympthom-door time of patients. Sympthom-door time may be decreased by spreading the usage of iv-tPA by neurologists in other hospitals or transporting AIS patients to center where patient can be treated. In 2018 AHA/ASA guidelines, it's recommended that patients with stroke findings should be transported to the closest center can administer iv-tPA(3). On the other hand, we have shorter door-needle time from other studies performed in Turkey(9,12). It's recommended that initial bolus dose of iv-tPA should be given to ≥50% of AIS patients within <60 minutes after arriving to hospital (door-needle time <60 minutes) (3). We found mean door-needle time < 60 minute. Additionally 94% of patients had door-needle time <60 minutes. We found high door-needle time in patients with poor clinical outcome, but there wasn't significant difference.

Our study showed that NIHSS score at 24th hour was significantly decreased in all patients. We found that NIHSS score at 24th hour decreased significantly in patients with good clinical outcome. Early neurological improvement after iv-tPAis accepted as predictor of recanalization and good clinical outcome(13). We found significant correlation between improvement in NIHSS score at 24th hour and good clinical outcome.

Our study showed that patients with good clinical outcome had high ASPECT scores. ASPECT score ≤7 points is predictor of poor clinical outcome(4). But there isn't any information about association between ASPECT score and clinical outcome in patients treated with iv-tPA in literature. In a recent trial, Das et al reported that lower ASPECT scores were associated with increased risk of ICH(14).

ICH rate was found as 6,4% in NINDS trial(1). In SITS-MOST trial, ICH was seen in 2,2% of patients(7). Hacke et al reported that 2,4% of patients treated with iv-tPA within 3-4,5 hours had ICH in ECASS III trial(2). In a meta-analysis evaluating ATLANTIS, ECASS and NINDS trials, substantial ICH rate was found as 5,9%(15). Kutluk et al found ICH rate as 4,9% in a multicenter study performed in Turkey(9). We found similar ICH rates with literature. Patients with ICH had decreased sympthom-door and increased door-needle times. There isn't any data about association between increased door-needle time and ICH. Cause of increased door-needle time might be prolonged treatment of high SBP levels. As known, iv-tPA is contraindicated in patient with SBP>180 mmHg and DBP>105 mmHg(3). These patients has resistant HT and we lost time while decreasing SBP and DBP.

Our study showed that increased SBP and glucose levels were associated with ICH after iv-tPA treatment. In previous studies, high levels of SBP were found as a predictor of ICH(16). In a recent trial, Nissar et al found increased SBP levels in patients with ICH(17). But there aren't many studies about association between SBP and ICH after iv-tPA treatment. In same study, serum glucose levels >185 md/dl were found as a predictor of ICH. It isn't known well how elevated serum glucose levels increase the risk of ICH. Mishiro et al reported that chronic hyperglycemia aggravated hemorrhagic transformation after ischemia-reperfusion injury by middle cerebral artery occlusion resulting with endotelial injury in diabetic mice(18). This can explain why high glucose levels increase the risk of ICH in AIS.

Our study had some limitations. Our study was designed as retrospectively. Our patient group was small and we didn't have control group. We didn't evaluated blood pressures during and after iv-tPA treatment.

Table 4: Demographic, Clinical, Radiological and Laboratory Findings of Patients With Good and Poor Clinical Outcome

	Good Outcome(%)	Poor Outcome(%)	p
n(%)	38(77,6)	11(23,4)	
Male	20(52,6)	8(72,7)	0,311
Age	64,7±12,2	76,8±6,9	0,062
Hypertension	28(73,7)	10(90,9)	0,415
Diabetes Mellitus	7(18,4)	3(27,3)	0,673
Smoking	16(42,1)	5(45,5)	1,000
Coronary Artey Disease	5(13,2)	3(27,3)	0,355
Hyperlipidemia	3(7,9)	3(27,3)	0,117
Stroke History	1(2,6)	4(36,4)	0,007
Atrial Fibrillation	12(31,6)	2(18,2)	0,475
Hearth Failure	2(5,3)	1(9,1)	0,542
Sympthom-needle time (min)	173±49	193±47	0,808
Sympthom-door time (min)	133±54	145±42	0,354
Door-needle time(min)	36±9	48±23	0,095
ASPECT	9,76±0,54	9,18±0,98	0,037
NIHSS at onset	7,6±3,7	10,6±4,5	0,121
NIHSS at 24th hour	3,2±2,2	10,5±7,8	0,001
Cardioembolism	12(31,6)	2(18,2)	0,475
Atherosclerosis	6(15,8)	1(9,1)	0,500
Lacunary infarction	9(23,7)	1(9,1)	0,419
Undefined cause	11(28,9)	7(63,6)	0,072
WBC(/mm^3)	8686±4569	7854±1790	0,222
Neutrophile %	62,9±15,7	60,9±11,3	0,275
Hemoglobin(gr/dl)	12,6±2,3	12,7±2,5	0,853
MCV(fl)	84,3±14,8	86,2±10,3	0,755
Platelet(/mm^3)	240078±79435	250454±57547	0,776
MPV(fl)	9,06±0,89	8,79±0,96	0,958
Glucose (mg/dl)	124±47	135±64	0,657
Urea (mg/dl)	37,7±20,4	40±10,9	0,134
Creatine(mg/dl)	0,91±0,42	0,97±0,29	0,250
AST(U/L)	43±120,8	25±12,9	0,442
ALT(U/L)	30,2±82,6	23±20,5	0,981
GGT(U/L)	30,5±41,7	39,9±34,7	0,449
INR	1,08±0,13	1,05±0,12	0,832
CRP(mg/l)	14,9±16,3	9,81±8,7	0,346
Triglyceride(mg/dl)	130,8±64,3	145,3±51,5	0,496
Total Kolesterol(mg/dl)	189,9±42,6	185,8±46,7	0,892
HDL(mg/dl)	42,5±14,5	41,2±6,2	0,245
LDL(mg/dl)	122,6±36,1	115,5±36,9	0,862
TSH(µU/ml)	2,78±6,86	2,79±2,56	0,188
T3(pg/ml)	2,61±0,46	2,41±0,48	0,748
T4(ng/ml)	1,25±0,24	1,13±0,11	0,029
HbA1c(%)	6,26±1,45	6,24±1,10	0,340
Systolic BP(mmHg)	136±23	170±34	0,257
Diastolic BP(mmHg)	78±14	90±18	0,125
Antiaggregant	17(44,7)	5(45,5)	1,000
Warfarin	3(7,9)	0(0)	1,000
ICH	1(2,6)	2(18,2)	0,122

CONCLUSION

Iv-tPA is an effective and confident method in treatment of AIS patients without LVO. This treatment reduces the mortality and disability due to AIS. Adminitration by experienced centers may reduce side effects of iv-tPA. Increasing centers which can treat patients with iv-tPA will reduce negative effects of AIS on public. More studies are needed about this topic.

Ethical approval: Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee (11.03.2021 / 2021/26)
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