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**Research Article**

# Identifying Risk Factors for rt-PA-related Intracerebral Hemorrhages in Patients with Acute Stroke

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## Summary

**Background and Purpose:** To evaluate risk factors for intracerebral hemorrhages and the clinical effects of these hemorrhages in patients treated with recombinant tissue plasminogen activator (rt-PA) for acute stroke.
**Methods:** In this prospective analysis, data were collected for patients with acute anterior circulation stroke who received intravenous (IV) rt-PA within 4.5 hours of symptom onset, after computed tomography (CT) between December 2008 and July 2013. Copies of head CT scans were obtained 24 hours after starting treatment. Intracerebral hemorrhages were classified according to the European-Australasian Acute Stroke Study (ECASS) classification. The definition of Safe Implementation of Thrombolysis in Stroke (SITS) was used for symptomatic intracerebral hemorrhage (sICH). The clinical outcomes of the patients were determined using the modified Rankin scale (mRS) at 90 days after treatment.
**Results:** Asymptomatic intracerebral hemorrhage (aICH) was observed in 50 (22.6%) of 221 patients and symptomatic intracerebral hemorrhage (sICH) was observed in 9 (4.1%). Multivariate analysis showed that the baseline glucose level and Alberta Stroke Program Early CT (ASPECT) score were associated with sICH. However, only the baseline ASPECT score was related to aICH. Patients with sICH and aICH both had higher mRS scores and mortality rates at 90 days compared with those without.
**Conclusions:** The presence of early ischemic changes on CT and hyperglycemia at the time of admission are independent risk factors for sICH in patients treated with IV rt-PA. Therefore, care must be taken in the evaluation and management of these factors.

**Key words:** Acute stroke, thrombolysis, rt-PA, intracerebral hemorrhage

# Akut İnmeli Hastalarda rt-PA ile İlişkili İntraserebral Hemorajiler İçin Risk Faktörlerinin Belirlenmesi

## Özet

**Amaç:** Rekombinant doku plazminojen aktivatörü (rt-PA) ile tedavi edilen akut inme hastalarında intraserebral kanamalar için risk faktörlerini ve bu kanamaların klinik etkilerini değerlendirmeyi amaçladık.
**Yöntemler:** Bu prospektif analizde, Aralık 2008 ve Temmuz 2013 tarihleri arasında, orta serebral arter iskemik inmesi tanısı ile semptom başlangıcı sonrası ilk 4,5 saat içerisinde bilgisayarlı tomografi (BT) görüntülemesinin ardından intravenöz (İV) rt-PA uygulanan hastaların verileri toplandı. Beyin BT incelemesi tedavi başlangıcından 24 saat sonra tekrarlandı. İntraserebral kanamalar European-Australasian Acute Stroke Study (ECASS) sınıflamasına göre sınıflandı. Semptomatik intraserebral kanama (SİSK) tanımı için Safe Implementation of Thrombolysis in Stroke (SITS) tanımı kullanıldı. Hastaların klinik

sonlanımları, tedaviden 90 gün sonra hesaplanan modified Rankin Scale (mRS) skoru ile belirlendi.
**Sonuçlar:** 221 hastanın 50'sinde (% 22,6) asemptomatik intraserebral kanama (AİSK), 9'unda (% 4,1) SİSK gözlendi. Çok değişkenli analizler bazal glukoz düzeyi ve Alberta Stroke Program Early CT (ASPECT) skorunun SİSK ile ilişkili olduğunu gösterdi. Buna rağmen, AİSK ile sadece ASPECT skoru ilişkiliydi. SİSK ve AİSK'sı olan hastalar, kanaması olmayan hastalara göre, 90. günde daha yüksek mRS skorları ve ölüm oranlarına sahipti.
**Sonuçlar:** Başvuru anında BT'de erken iskemik değişikliklerin varlığı ve hiperglisemi, IV rt-PA ile tedavi edilen hastalarda SİSK için bağımsız risk faktörleridir. Bu nedenle bu faktörlerin değerlendirilmesinde ve yönetiminde dikkatli davranılmalıdır.

**Anahtar Kelimeler:** Akut inme, tromboliz, rt-PA, intraserebral kanama

## INTRODUCTION

Despite some limitations such as the time factor or contraindications, intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is one of the proven and approved treatments for acute ischemic stroke. The fear of symptomatic intracerebral hemorrhage (sICH) as a complication of this treatment, prevents the widespread use of this life-saving, disability-reducing treatment.

IV rt-PA may increase ischemic neurotoxicity, blood-brain barrier damage, edema and cerebral hemorrhage (1). The main question in revascularization practice is whether hemorrhagic transformation is related to reperfusion and biochemical pathways or to lysis (2).The incidence of sICH was not clear and was found in a wide range of 6.4-19.5% in different clinical trials (3).The probable cause of these inconsistencies with sICH rates is the use of different clinical and radiologic definitions of sICH in different studies (4).

Previous studies identified some risk factors for sICH such as advanced age, early ischemic changes, elevated mean arterial blood pressure before treatment and a history of diabetes mellitus (DM) or cardiac disease (5,6). We aimed to evaluate risk factors for rt-PA-related intracerebral hemorrhages and the clinical effects of these hemorrhages in patients with acute anterior circulation stroke.

## MATERIAL AND METHODS

Data were collected prospectively on consecutive patients with acute anterior circulation stroke who received IV rt-PA within 4.5 hours of symptom onset between December 2008 and July 2013 at Eskişehir Osmangazi University Stroke Center. IV rt-PA was given according to the European Stroke Organization guidelines (7). Patients treated with mechanical thrombectomy or intra-arterial rt-PA were excluded from the analysis.

Demographic features, the time between symptom onset and thrombolytic treatment, baseline variables including National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT (ASPECT) score, serum glucose and arterial blood pressure level were obtained, and the modified Rankin scale (mRS) score was assessed at 90 days. Computed tomography (CT) was performed before thrombolysis and within 24 hours of thrombolysis or immediately in the event of clinical deterioration. Intracerebral hemorrhages were classified radiologically according to the European-Australasian Acute Stroke Study (ECASS) classification: "hemorrhagic infarct type 1 (HI-1), small petechiae along the margins of the infarct; hemorrhagic infarct type 2 (HI-2), confluent petechiae within the infarcted area but no space occupying effect; parenchymal hemorrhage type 1 (PH-1), blood clots in <30 % of the infarcted area with some slight space-occupying effect; and parenchymal

hemorrhage type 2 (PH-2), blood clots in >30% of the infarcted area with a substantial space-occupying effect" (8). We used the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition for sICH: "type 2 parenchymal hemorrhage on imaging 22 to 36 hours after treatment or earlier if an imaging scan was performed due to clinical deterioration combined with a neurologic deterioration of >4 NIHSS points from baseline or from the lowest NIHSS score between baseline and 24 hours or leading to death within 24 hours" (9).

**Statistical Analyses**

The patients treated with rt-PA were classified into 2 major groups: those with intracerebral hemorrhage (ICH) and those without. This grouping was performed separately for patients with sICH or asymptomatic intracerebral hemorrhage (aICH), and the clinical, demographic, and radiographic data of the groups were compared. For normally distributed continuous variables, mean and standard deviation were used. Independent samples were analyzed using the t test. Median value, and 25th and 75th percentile values were used for unevenly distributed variables and these variables were analyzed using the Mann-Whitney U test. Categorical variables were compared using the chi square test. All statistical analyses were performed with IBM SPSS Statistics 20.0 and Minitab 16 package programs. Logistic regression analysis was used to determine the risk factors for intracerebral hemorrhage. A level of $p<0.05$ was accepted as statistically significant.

**RESULTS**

A total of 221 patients treated with rt-PA were included in the study. The mean age of the patients was 65.2±11 years and the mean NIHSS score at the time of admission was 15.36± 4.5. The ASPECT score at admission was 8 or over in 83.3% of patients.

aICH was observed in 50 (22.6%) of 221 patients and sICH was observed in 9 (4.1%). Figure 1 shows some of the CT images of patients with sICH. Overall, hemorrhagic infarct type 1 occurred in 35 (59.3%), hemorrhagic infarct type 2 occured in 12 (20.3%), parenchymal hemorrhage type 1 was observed in 3 (5%), and parenchymal hemorrhage type 2 was seen in 9 (15.3%) patients (Table 1). All patients with PH-2 fulfilled the SITS-MOST criteria for sICH. At the same time, 2 patients with PH-1 and 1 patients with HI-1 had a neurologic deterioration of >4 NIHSS points from baseline or from the lowest NIHSS score or died within 24 hours as specified in SITS-MOST definition. However, these hemorrhages were not considered as sICH because they do not fulfill the SITS-MOST criteria for the type of hemorrhage.

The demographic and clinical characteristics of patients with aICH were compared with those of patients with no hemorrhage. For this reason, patients with sICH were excluded from the analysis. Patients with aICH had higher NIHSS scores and serum glucose levels compared with those with no hemorrhage ($p=0.023$ and $p=0.019$, respectively), and were more likely to have a lower ASPECT score ($p<0.001$). Furthermore, after 90 days of thrombolysis, the mRS scores and mortality rates of these patients were higher than those with no hemorrhage ($p=0.002$ and $p=0.009$, respectively). The presence of good outcome (mRS 0-1) was more common in patients with no hemorrhage compared with patients with aICH ($p=0.017$). There was no significant difference in the other demographic and clinical variables (Table 2).

The demographic and clinical characteristics of patients with sICH were compared with those of patients without sICH. Patients with sICH had lower ASPECT scores before treatment ($p=0.014$). These patients also had significantly higher mRS scores and

mortality rates at 90 days than those without sICH (p=0.001 and p=0.031, respectively). Good outcome (mRS 0-1) was not observed in any patients with sICH, whereas it was observed in 43.6 % of those without sICH (p=0.011). Poor outcome (mRS 3-6) was observed in all patients with sICH, whereas it was observed in 48.6% of patients without sICH (p=0.003). No differences in other baseline demographic and clinical variables were observed (Table 3).

According to the multivariate analysis performed separately in patients with aICH and sICH, when the baseline ASPECT score increased by one unit; the rate of sICH and aICH were reduced by 4.65 times and 1.37 times, respectively (p=0.037 and p=0.024).Furthermore, when the baseline blood glucose level increased by one unit (1 mg/dL); the probability of sICH was increased by 1.018 fold (p=0.038) (Table 4).

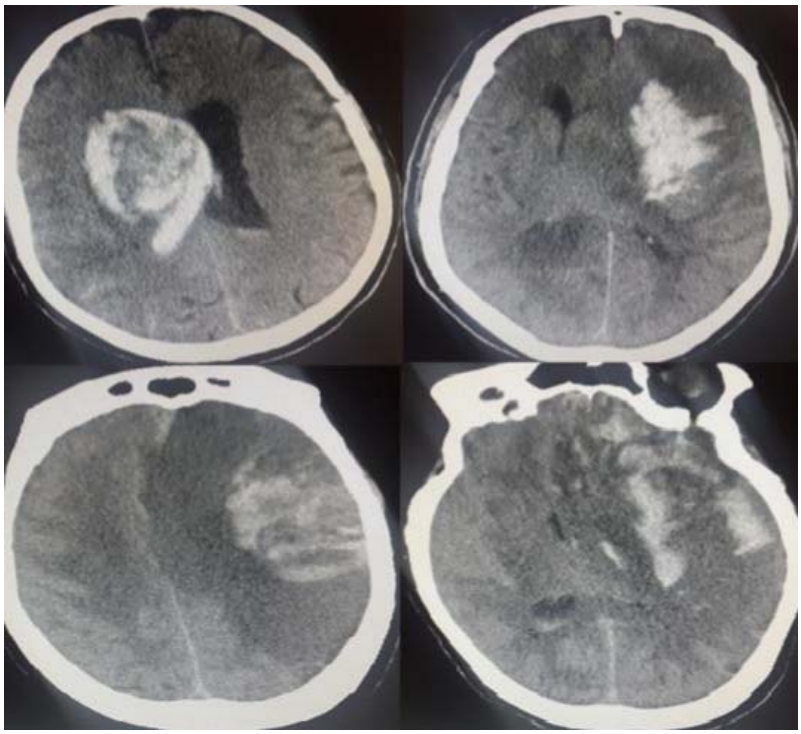

***Figure 1.*** *Some CT images of patients with sICH.*

**Table 1.** Clinical variables of all patients after thrombolysis.

| Variable | | | n* | % |
|---|---|---|---|---|
| aICH | Yes | | 50 | 22.6 |
| sICH | Yes | | 9 | 4.1 |
| Type of bleeding | | HI-1 | 35 | 59.3 |
| | | HI-2 | 12 | 20.3 |
| | | PH-1 | 3 | 5.0 |
| | | PH-2 | 9 | 15.3 |
| GI bleeding | Yes | | 2 | 0.9 |
| Angioedema | Yes | | 0 | 0.0 |
| mRS 0-1 | Yes | | 92 | 41.8 |
| mRS 0-2 | Yes | | 107 | 48.6 |
| mRS 3-6 | Yes | | 112 | 50.9 |
| Mortality | Yes | | 33 | 15.0 |

*****One patient could not be assessed for mRS score and mortality.
aICH= asymptomatic intracerebral hemorrhage; sICH= symptomatic intracerebral hemorrhage; HI-1= hemorrhagic infarct type 1; HI-2= hemorrhagic infarct type 2; PH-1= parenchymal hemorrhage type 1; PH-2= parenchymal hemorrhage type 2; GI= gastrointestinal; mRS = modified Rankin scale

**Table 2.** Comparison of demographic and clinical variables in patients with and without aICH

| Variable | aICH | | *P* |
|---|---|---|---|
| | Positive (n=50) | Negative (n=162)* | |
| Male, % | 52.0 | 54.9 | 0.840 |
| Age, median | 70.0 | 67.0 | 0.068 |
| Baseline NIHSS, median | 18.0 | 15.5 | 0.023 |
| Baseline ASPECTs, median | 8.0 | 9.0 | <0.001 |
| Baseline serum glucose (mg/dL), median | 141.0 | 120.5 | 0.019 |
| Diabetes mellitus, % | 28.0 | 33.3 | 0.594 |
| Baseline SBP, median | 145.0 | 144.0 | 0.538 |
| Hypertension, % | 66.0 | 63.6 | 0.886 |
| Antiplatelet, % | 28.0 | 29.6 | 0.965 |
| Time to thrombolysis (min), median, | 140.0 | 150.0 | 0.414 |
| mRS (at 90 days), median | 4.0 | 2.0 | 0.002 |
| mRS 0-1, % | 28.0 | 48.5 | 0.017 |
| mRS 0-2, % | 53.4 | 50.6 | 0.212 |
| mRS 3-6, % | 60.0 | 45.3 | 0.099 |
| Mortality, % | 26.0 | 9.9 | 0.009 |

*One patient could not be assessed for mRS score and mortality.
aICH= asymptomatic intracerebral hemorrhage; NIHSS= National Institutes of Health Stroke Scale; ASPECTs= Alberta Stroke Program Early CT score; SBP= systolic blood pressure; mRS= modified Rankin scale

**Table 3.** Comparison of demographic and clinical variables in patients with and without sICH

| | sICH | | |
|---|---|---|---|
| Variable | Positive (n=9) | Negative (n=212)* | *P* |
| Male, % | 66.7 | 54.3 | 0.517 |
| Age, median | 70.0 | 68.0 | 0.660 |
| Baseline NIHSS, median | 18.0 | 16.0 | 0.200 |
| Baseline ASPECTs, median | 8.0 | 9.0 | 0.014 |
| Baseline serum glucose (mg/dL), median | 151.0 | 125.0 | 0.072 |
| Diabetes mellitus, % | 55.6 | 32.0 | 0.160 |
| Baseline SBP, median | 140.0 | 145.0 | 0.858 |
| Hypertension, % | 88.9 | 64.2 | 0.167 |
| Antiplatelet, % | 55.6 | 29.2 | 0.134 |
| Time to thrombolysis (min), median, | 154.4 | 147.5 | 0.397 |
| mRS (at 90 days), median | 5.0 | 2.0 | <0.001 |
| mRS 0-1, % | 0 | 43.6 | 0.011 |
| mRS 0-2, % | 0 | 50.7 | 0.008 |
| mRS 3-6, % | 100 | 48.6 | 0.003 |
| Mortality, % | 44.4 | 13.7 | 0.031 |

*One patient could not be assessed for mRS score and mortality.
sICH= symptomatic intracerebral hemorrhage; NIHSS= National Institutes of Health Stroke Scale; ASPECTs= Alberta Stroke Program Early CT score; SBP= systolic blood pressure; mRS= modified Rankin scale

**Table 4.** Results of multivariate analysis

| Variable | Regression Coefficient | Estimated odds ratio | 95 % CI | *P* |
|---|---|---|---|---|
| aICH | | | | |
| Baseline ASPECTs | -0.674 | 0.509 | 0.284-0.915 | 0.024 |
| sICH | | | | |
| Baseline ASPECTs | -1.537 | 0.215 | 0.051-0.912 | 0.037 |
| Baseline serum glucose (mg/dL) | 0.018 | 1.018 | 1.001-1.035 | 0.038 |

CI= confidence interval; aICH= asymptomatic intracerebral hemorrhage; ASPECTs= Alberta Stroke Program Early CT score; sICH= symptomatic intracerebral hemorrhage

## DISCUSSION

In our study, the overall rate of sICH was found as 4.1%. The sICH rates of other studies were examined, and this ratio was found as 6.4% in the National Institute of Neurological Disorders and Stroke tPA Stroke Study (NINDS), 6.2% in the European-Australasian Acute Stroke Study (ECASS) II, and 1.7% in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) (5, 8, 10). Another study found that the sICH rate could be in the range of 2.7-15.7% (11). The frequency of sICH related to rt-PA is not clear. The discrepancy is probably based on the differences of sICH definitions and application procedures. The sICH rate in our study is consistent with rates in previous studies.

We found that the mRS scores and mortality rates of patients with sICH were significantly higher than those without. The association of sICH with poor functional outcome is clearly known. In ECASS II, a similar relationship was observed between sICH and poor functional outcome. Furthermore, in the second part of NINDS, the mortality rate in the sICH group was 10 times higher than in the placebo group(12). In light of these studies, it is appropriate to claim that sICH is a poor prognostic factor.

The rate of aICH was found as 22.6% in the present study. In ECASS I and II, this rate was 30% and 29.5%, respectively (13,14). In NINDS, the rate of aICH was similar between the placebo and rt-PA group (15). We found that patients with aICH were more likely to have a worse outcome than those without. In addition, the presence of good outcome was more often in patients without aICH in our study; this result is parallel to the results of the study of Dzialowski et al., which suggested that asymptomatic hemorrhage might not be benign (13). In contrast to our observations, Molina et al. demonstrated that hemorrhagic infarct was a marker of early reperfusion, reduced infarct volume, and was associated with good functional outcome (16). Some other studies also supported this hypothesis (8,17). aICH appears to be a poor prognostic factor in our analysis however, it may be associated with the severity of infarction, delayed reperfusion, continuation of vessel occlusion or prolonged ischemia (13). Therefore, aICH may be a marker of poor prognostic factors. In accordance with this hypothesis, we showed that patients with

aICH were more likely to have a higher NIHSS score on admission, which suggests that aICH might be the result of severe stroke.

From the multivariate analysis of our data, rates of both sICH and aICH were reduced by the increasing ASPECT score on admission. This relationship was more apparent for sICH. In previous studies, early ischemic changes were identified as a risk factor for sICH (8,15,18). Based on the literature, the decision for thrombolysis should be made carefully in patients with prevalent ischemic changes and the onset time of the symptoms should be questioned thoroughly.

Elevated arterial blood pressure has been associated with intracerebral hemorrhages after thrombolysis (19,20). In our study, arterial blood pressure was not evaluated at the time of admission. First, the arterial blood pressure was reduced to a certain level with medication and then subsequent measurements were recorded in the analysis. The result might be different if the arterial blood pressure was analyzed at the time of the admission, not before treatment.

In our study, elevated serum glucose was associated with aICH and a similar correlation was detected for sICH in the multivariate analysis. Previously, two large studies found hyperglycemia as a significant risk factor for sICH (5,21). A similar relationship was also observed in the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR) study (22). Hyperglycemia and DM may damage microvascular structures and thus lead to post-reperfusion edema and hemorrhagic transfusion (5). In animal models, hyperglycemia has been shown to cause hemorrhagic transformation of cerebral infarction by enlarging blood-brain barrier damage (23,24). Furthermore, it may increase blood brain barrier deterioration by increasing matrix metalloproteinase (MMP)-9 expression (2). It was considered that the presence of hyperglycemia might enhance the harmful effects of thrombolytics such as hemorrhage (25). Therefore, protocols related to serum glucose should be strictly performed before, during, and after rt-PA.

One of the limitations of our study was the small cohort size of patients with sICH. Accordingly, we may have overlooked some statistically significant risk factors. However, we can claim that our results are similar to those of major stroke centers. Additionally, in our analysis, we assessed arterial blood pressure that lowered to a certain level before rt-PA. Thus, some risk factors may have been deemed less important than they actually merit.

In conclusion, the rate of sICH, which is the major complication of IV rt-PA, was found within the limits expected from previous studies. Early ischemic changes on CT and elevated serum glucose level before treatment were identified as independent risk factors for sICH, and the importance of the evaluation and intervention of these risk factors should again be underlined.

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