Comparison of Blood Pressure Changes during the First 24 Hours after Tissue Plasminogen ActivatorAdministration in Patients with and without Intracerebral Hemorrhage

Mohammadzadeh Vardin H. MD[1*], Taher Aghdam A. A. MD[2], Farhodi M. MD[2], Sadeghi Hekmabadi E. MD[2]

Abstract:

Background and Objective: Recent studies have highlighted the importance of temporal blood pressure indices, including mean and peak blood pressure during the 2–8-hour, 8–24-hour, and overall 24-hour periods, in predicting the risk of hemorrhage and severe complications. Despite considerable advances in this field, a substantial gap remains in the evidence regarding the effect of blood pressure fluctuations on the occurrence of hemorrhages requiring neurosurgical intervention following administration of the thrombolytic agent alteplase. The present study aimed to address this issue through a detailed evaluation of data from patients admitted to a dedicated stroke care unit (SCU).

Materials and Methods: This retrospective study included all patients with ischemic stroke admitted to the SCU of Imam Reza Hospital, Tabriz University of Medical Sciences, between 2020 and 2022. Eligibility criteria required complete clinical and paraclinical data, no prior use of anticoagulant medications or contraindications to thrombolytic therapy, and accurate blood pressure recordings during the first 24 hours following alteplase administration. Blood pressure was recorded every 15 minutes during the first 2 hours, every 30 minutes for the subsequent 6 hours, and then hourly until the completion of the first 24 hours; these data were extracted from medical records. Variables assessed included age, sex, blood pressure values, and the frequency of blood pressure measurements. Symptomatic intracerebral hemorrhage was defined as parenchymal hematoma type 2. Chi-square and independent-samples t-tests were used for comparisons, with a p-value less than 0.05 considered statistically significant.

Results: Comparison of systolic blood pressure changes between the hemorrhage and non-hemorrhage groups after TPA administration showed no statistically significant difference at hospital admission (P = 0.998). However, systolic blood pressure changes were significantly greater in the hemorrhage group during the first 2 hours (P = 0.048) and during the 2-to-8-hour period (P = 0.004). No statistically significant difference was observed between the two groups during the 8-to-24-hour period (P = 0.879). Diastolic blood pressure at hospital admission also did not differ significantly between groups (P = 0.852), and no significant between-group difference was found during the first 2 hours (P = 0.524). In contrast, diastolic blood pressure during the 2-to-8-hour period was significantly higher in the hemorrhage group than in the non-hemorrhage group (P = 0.004). No statistically significant difference in diastolic blood pressure was observed between groups during the 8-to-24-hour period (P = 0.744).

Conclusion: This study demonstrated that patients who developed intracerebral hemorrhage following thrombolysis exhibited higher diastolic blood pressure during the first 24 hours compared to other patients, while the difference in systolic blood pressure was not statistically significant overall. Surgical and pharmacological interventions were performed according to the severity and location of the hemorrhage, as well as the patients' clinical condition. These findings underscore the importance of close blood pressure monitoring and individualized therapeutic decision-making in preventing thrombolysis-related complications.

Keywords: Blood Pressure; Fibrinolytic Agents; Ischemic Stroke; Tissue Plasminogen Activator; Cerebral Hemorrhage

[1] Neurologist, Tabriz University of Medical Sciences, Imam Reza Hospital
[2] Professor of Neurology, Tabriz University of Medical Sciences, Imam Reza Hospital
Received: 21/2/2026
Accepted: 1/6/2026

Corresponding Author: Dr. Hanieh Mohammadzadeh Vardin

Tel: 041-33353639
E-mail: Haniyeh.mohammadzadev@gmail.com

Please Cite this Article as:
Mohammadzadeh Vardin H, Taher Aghdam A. A, Farhodi M, Sadeghi Hekmabadi E. Comparison of Blood Pressure Changes during the First 24 Hours after Tissue Plasminogen ActivatorAdministration in Patients with and without Intracerebral Hemorrhage. Iranian Journal of Surgery. 2026; 34 (2): 39-48. doi:10.22034/ijs.2026.741846

Background and Objective

Acute ischemic stroke is one of the leading causes of death and neurological disability worldwide, accounting for a substantial proportion of the global burden of cerebrovascular disease.[1] Each year, millions of individuals are affected by this condition, which results from the sudden occlusion of a cerebral artery and leads to severe impairment of cerebral blood flow.[2] The administration of alteplase, a thrombolytic agent, remains the standard treatment for eligible patients and offers the greatest chance of neurological recovery.[3] However, alteplase therapy is associated with an increased risk of intracerebral hemorrhage, a complication that may lead to serious and potentially fatal clinical outcomes.[4]

Intracerebral hemorrhage following alteplase administration most commonly occurs due to reperfusion of ischemic tissue, microvascular fragility, and activation of tissue-destructive pathways.[5] Blood pressure is considered a key dynamic factor in this process, as significant elevations or fluctuations during the early hours after thrombolysis may increase the likelihood of rupture of damaged capillaries.[6] Previous studies have shown that both the magnitude and trajectory of blood pressure changes within the first 24 hours after alteplase administration are directly associated with the occurrence of parenchymal hematoma type 2, which is regarded as the most severe form of hemorrhagic transformation.[7]

Blood pressure management during this period is particularly challenging because of the need to balance the preservation of perfusion in the ischemic penumbra with the prevention of hemorrhagic complications.[8] Elevated systolic blood pressure may enhance perfusion to vulnerable brain regions; however, excessive reduction can contribute to the expansion of the infarcted area.[9] The role of diastolic blood pressure has received less attention, although available evidence suggests that early elevation in diastolic pressure may sustain mechanical stress on fragile capillary walls, thereby increasing the risk of hemorrhage progression.[10]

In some patients, extensive hemorrhage or a high-volume hematoma creates a clinical scenario in which conservative treatment is insufficient, necessitating neurosurgical intervention such as craniotomy or hematoma evacuation.[11] Surgical decision-making after alteplase administration is highly sensitive because large hematomas can produce a substantial mass effect and rapidly elevate intracranial pressure.[12] In this context, identifying the pattern of blood pressure changes during the first 24 hours and clarifying their relationship with hemorrhage severity and the need for surgery may improve both prediction and clinical management.[13]

Recent investigations have emphasized the importance of time-based blood pressure indices, including mean blood pressure and peak blood pressure during the 2-to-8-hour, 8-to-24-hour, and full 24-hour periods, in predicting the risk of hemorrhage and severe complications.[14] Despite these advances, a considerable gap remains in the current evidence regarding the relationship between blood pressure changes and the occurrence of hemorrhage requiring neurosurgical intervention after alteplase administration. Therefore, the present study was conducted to compare blood pressure changes during the first 24 hours following TPA administration between patients with and without intracerebral hemorrhage.

Materials and Methods

Study Design

This retrospective study reviewed the medical records of all patients with ischemic stroke admitted to the Stroke Care Unit (SCU) at Imam Reza Hospital, affiliated with Tabriz University of Medical Sciences, from the beginning of 2020 through the end of 2022.

Sampling

The initial sample size was estimated to be approximately 300 patients. However, because of the available data and the absence of complete blood pressure charts in some records, a total of 268 patients were

ultimately included in the study. These patients had received thrombolytic therapy over the three-year study period, of whom 35 developed intracerebral hemorrhage following thrombolysis. All 268 eligible patients were enrolled using a census sampling method.

Eligibility Criteria

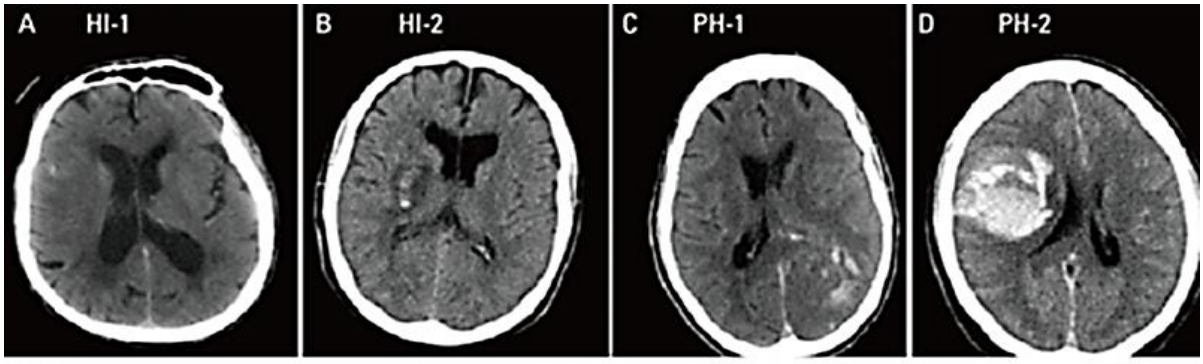
Only records containing complete clinical and paraclinical information were included in the analysis. The study population consisted of all patients with ischemic stroke admitted to the SCU of Imam Reza Hospital who received intravenous alteplase thrombolysis based on the National Institutes of Health Stroke Score (NIHSS) and other predefined clinical and paraclinical criteria. In all cases, thrombolytic therapy was administered by the same treatment team following standard institutional protocols.

Patients were excluded if they had received anticoagulant medications prior to admission, had any medical contraindications to thrombolytic therapy, or lacked accurate and consecutive blood pressure recordings in the nursing chart during the first 24 hours after TPA administration.

Study Procedure

In this retrospective cross-sectional study, we reviewed the records of all patients with ischemic stroke admitted to the SCU of Imam Reza Hospital between 2020 and 2022. Eligible patients were those who received thrombolysis according to NIHSS score and other predefined criteria, and whose blood pressure records from the first day were available. These records were analyzed to assess post-treatment hemorrhage and blood pressure changes during the first 24 hours following therapy.

Blood pressure was measured every 15 minutes during the first 2 hours after injection, every 30 minutes for the subsequent 6 hours, and then hourly up to 24 hours. These measurements were documented on blood pressure monitoring charts and are available in the patients' medical records. The variables examined included patient age, sex, blood pressure values, and the number of blood pressure recordings. In this study, symptomatic intracerebral hemorrhage (sICH) was defined as parenchymal hematoma type 2, as illustrated in Figure 1. Patients were categorized into two groups according to the presence or absence of intracerebral hemorrhage after TPA administration (Figure 1).



A	Hemorrhagic infarction - 1	Isolated petechial staining of infarcted tissue without mass effect
B	Hemorrhagic infarction - 2	Onfluent patechiae in infarcted tissue without mass effect
C	Parenchymal Hemorrhage - 1	Homogeneous high attenuation lesion with minimal mass effect occupying less than 30% of the infarcted area
D	Parenchymal Hemorrhage - 2	Lesion occupying more than 30% of the infarcted area with definite mass effect Possible extension of hemorrhage into the ventricular space, Aswell as any hemorrhage outside the infracted area

Figure 1. Types of intracerebral hemorrhage (ICH) evaluated in the present study.

Statistical Analysis

Data were analyzed using SPSS version 22. Results are presented as numbers (percentages), means ± standard deviation, or medians (interquartile ranges), depending on the distribution characteristics of the variables. Given the non-normal distribution of some variables, appropriate descriptive statistics were selected. The chi-square test was used to compare qualitative demographic and baseline variables between the two groups, while the independent-samples t-test was applied to compare quantitative variables. Additionally, the independent-samples t-test was used to compare systolic and diastolic blood pressure between the two groups at different time points. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study was conducted after obtaining approval from the Research Council of the Faculty of Medicine and Tabriz University of Medical Sciences, as well as ethics approval under the code IR.TBZMED.REC.1402.196, dated 08/03/1402. Prior to the initiation of the study, the researcher and the study objectives were introduced to Imam Reza Educational and Medical Center, and necessary coordination was made with the head of the relevant department. Study participants were carefully selected according to predefined criteria to enhance the validity of the findings, and all study procedures were performed in full compliance with standard methodological requirements. Reliable scientific sources were used in preparing the thesis discussions, and the results will be presented and published for clinical application. Given the retrospective nature of the study, written informed consent was not obtained from participants; ethics approval was considered sufficient to serve as a waiver of informed consent.

Results

The initial sample size was estimated to be approximately 300 patients; however, due to data availability and the absence of blood pressure charts in some medical records, 268 patients were ultimately included in the study. Overall, 9 patients (3.3%) developed symptomatic intracerebral hemorrhage, defined as parenchymal hematoma type 2, while 26 patients (9.7%) developed asymptomatic hemorrhage. This latter group included 11 patients (4.1%) with hemorrhagic transformation and 15 patients (5.5%) with parenchymal hematoma type 1.

The mean age of patients who received thrombolysis was 71.7 ± 4.2 years in the hemorrhage group and 67.3 ± 3.3 years in the non-hemorrhage group. No statistically significant difference in age was observed between the two groups ($P = 0.058$). Intracerebral hemorrhage occurred in 17 women (13.6%) and 18 men (12.6%). In contrast, 108 women (86.4%) and 125 men (87.4%) did not develop hemorrhage. There was no statistically significant difference in sex distribution between patients with and without hemorrhage ($P = 0.806$).

Regarding discharge status, 16 patients with hemorrhage (45.7%) died, 16 patients (45.7%) were discharged per physician order, 2 patients (5.7%) were discharged against medical advice, and 1 patient (2.9%) was transferred to another center. A statistically significant association was observed between discharge status and hemorrhage, with mortality being significantly higher among patients who developed hemorrhage compared to those without hemorrhage ($P < 0.001$).

Among patients with non-lacunar stroke, 35 (13.8%) developed hemorrhage, whereas none of the patients with lacunar stroke experienced hemorrhage. However, no statistically significant association was found between lacunar stroke and the occurrence of intracerebral hemorrhage in the study population ($P = 0.231$).

In all 13 patients (100%), thrombolysis was administered within one hour of symptom onset, and none developed hemorrhage. The incidence of hemorrhage was 11.7% (9 patients) among those who received thrombolysis within 1–2 hours, 12.4% (12 patients) among those treated 2–3 hours after symptom onset, and 17.3% (14 patients) among those treated 3–4.5 hours after symptom onset. Although the rate of intracerebral hemorrhage increased as the interval between symptom onset and

thrombolysis became longer, no statistically significant association was observed between the time from symptom onset to thrombolysis and the occurrence of hemorrhage (*P* = 0.389).

Among patients who developed intracerebral hemorrhage following intravenous thrombolysis, interventional and surgical procedures were performed according to hemorrhage severity, location, and the patients' clinical status. Two patients underwent surgical hematoma evacuation to reduce intracranial pressure and prevent further tissue injury. Additionally, decompressive craniectomy was performed in two other patients because of increased intracranial pressure and life-threatening clinical deterioration. Only one patient, who had extensive intracerebral hemorrhage with obstruction of cerebrospinal fluid flow, underwent shunt placement. Another patient received external ventricular drain (EVD) placement because of acute hydrocephalus secondary to intraventricular hemorrhage.

Regarding pharmacological treatment, antifibrinolytic therapy was administered to five patients with intracerebral hemorrhage (14.3%) to control bleeding and enhance hemostasis. In contrast, the majority of patients—30 individuals (85.7%)—did not receive this treatment. This pattern reflects a targeted selection of interventions based on each patient's clinical condition and imaging findings (Figure 2).

Comparison of systolic blood pressure changes between the hemorrhage and non-hemorrhage groups after TPA administration showed that systolic blood pressure at hospital admission did not differ significantly between the two groups (*P* = 0.998). However, systolic blood pressure changes were significantly greater in the hemorrhage group during the first 2 hours (*P* = 0.048) and during the 2-to-8-hour period (*P* = 0.004). In contrast, no statistically significant difference was observed between the two groups during the 8-to-24-hour period (*P* = 0.879) (Figure 3).

A comparison of diastolic blood pressure changes between the hemorrhage and non-hemorrhage groups after TPA administration revealed no significant difference in diastolic blood pressure at hospital admission (*P* = 0.852). Changes during the first 2 hours were also not statistically significant (*P* = 0.524). However, diastolic blood pressure during the 2-to-8-hour period was significantly higher in the hemorrhage group than in the non-hemorrhage group (*P* = 0.004). In addition, no statistically significant difference in diastolic blood pressure was observed between the two groups during the 8-to-24-hour period (*P* = 0.744) (Figure 4).

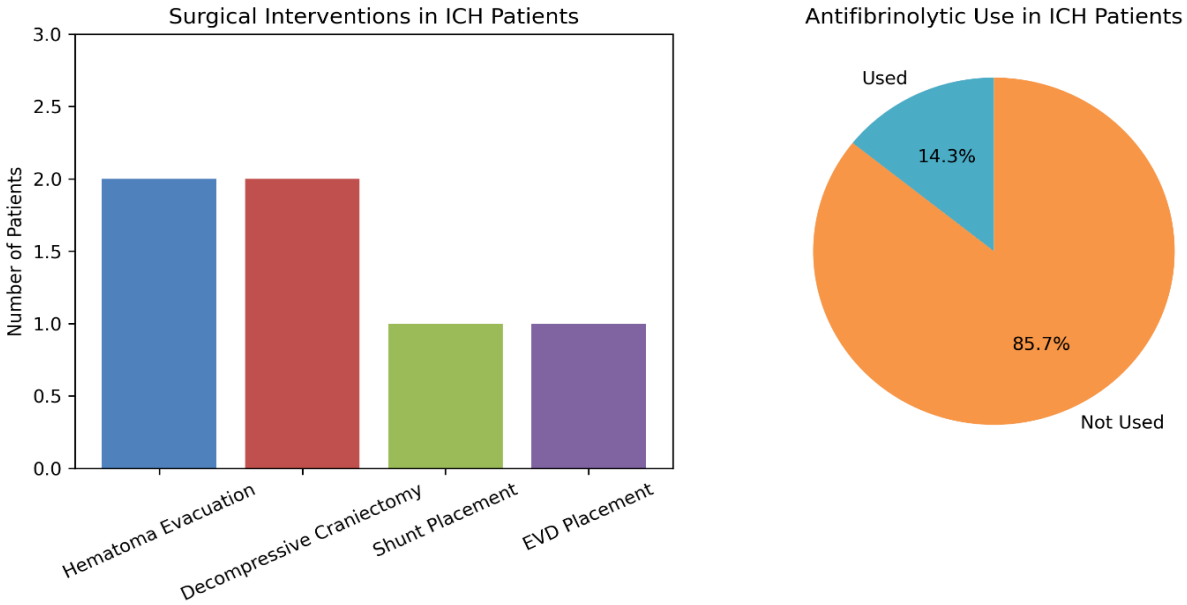


Figure 2. Distribution of interventional and surgical procedures among patients with intracerebral hemorrhage following intravenous thrombolysis.

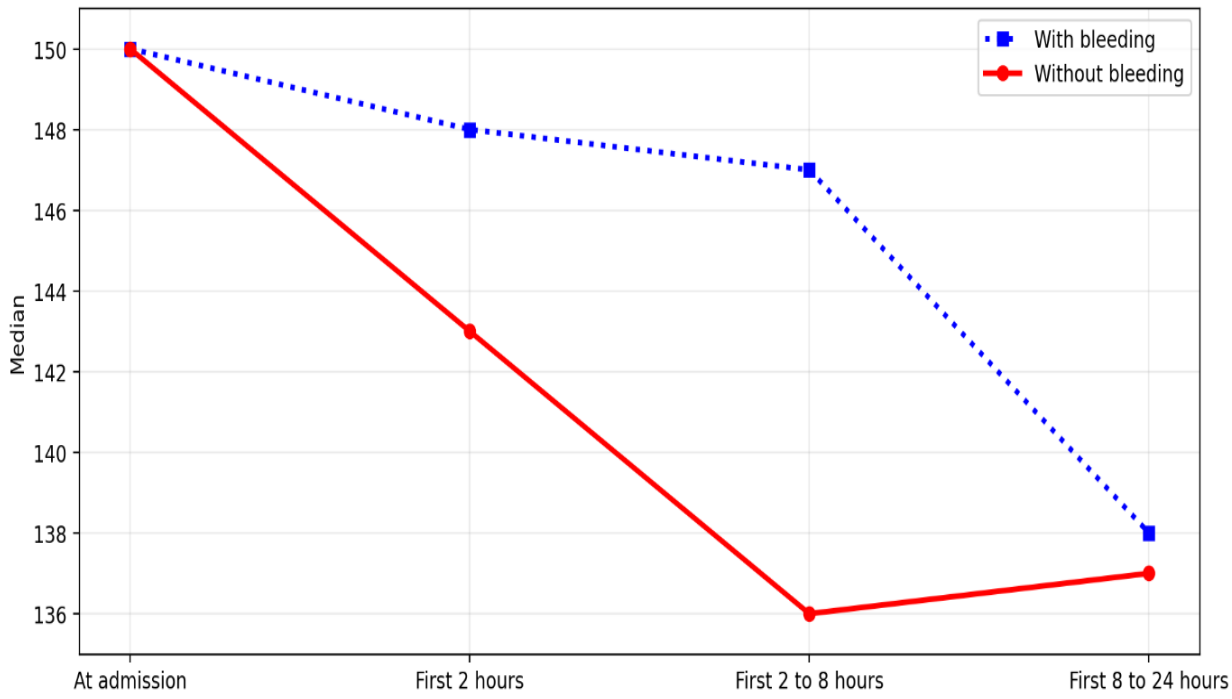


Figure 3. Comparison of systolic blood pressure changes in alteplase-treated patients with and without intracerebral hemorrhage.

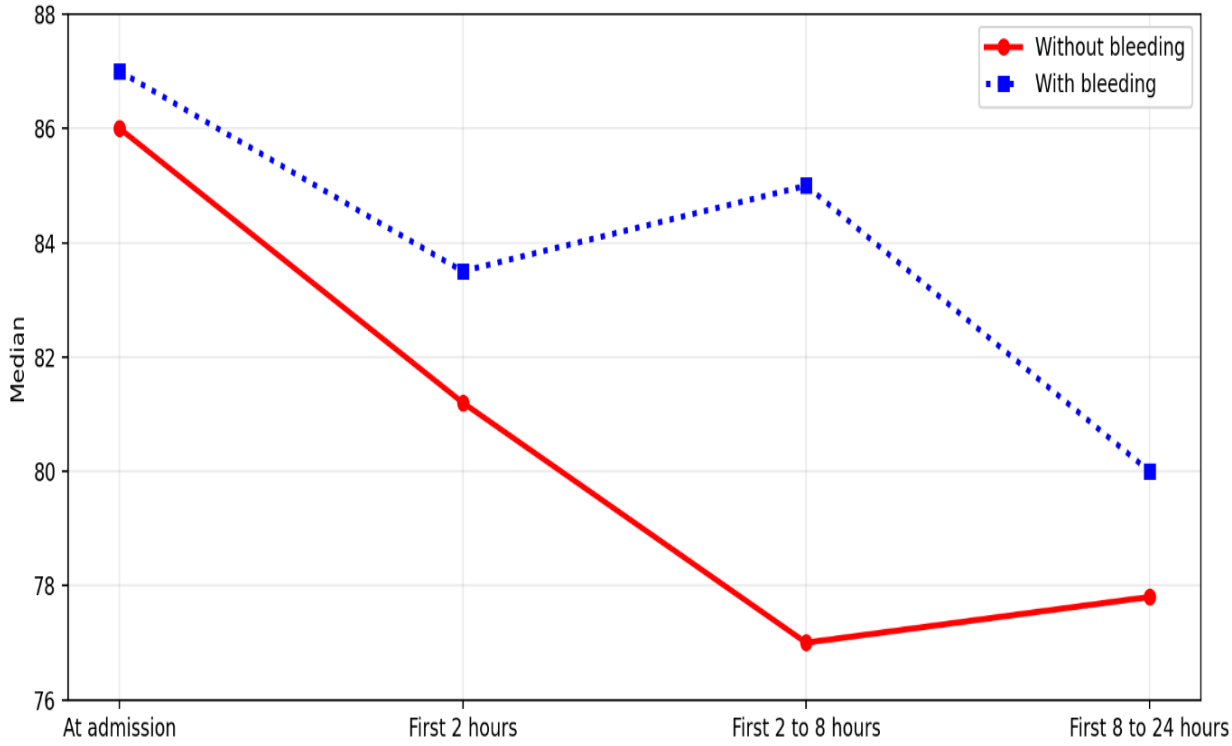


Figure 4. Comparison of diastolic blood pressure changes in alteplase-treated patients with and without intracerebral hemorrhage.

Discussion

Intracerebral hemorrhage after intravenous thrombolysis with alteplase is considered one of the most serious and potentially fatal complications of this treatment. Its occurrence has been attributed, in previous studies, to a complex interplay of clinical, hemodynamic, and pathophysiological factors.[6] The principal mechanism is thought to involve acute disruption of the blood–brain barrier secondary to the initial ischemic insult, activation of inflammatory pathways, and the release of matrix metalloproteinases such as MMP-9.7 In addition to its fibrinolytic action, alteplase may indirectly affect the vascular endothelium, increase vascular permeability, and thereby facilitate hemorrhagic transformation.[8]

Blood pressure levels during the early hours after thrombolysis represent a key determinant of cerebrovascular hemodynamic stability. Elevated blood pressure, particularly in the diastolic range, can increase the transvascular pressure gradient and, when the blood–brain barrier is compromised, promote uncontrolled extravasation of plasma and blood cells into the brain parenchyma.[9] This phenomenon, commonly known as hyperperfusion injury, may aggravate vascular damage and ultimately result in hemorrhage.[10] Furthermore, significant blood pressure variability—even when mean values are comparable—can cause rapid fluctuations in vascular shear stress, potentially triggering rupture of structurally weakened microvessels or ischemia-related microaneurysms.[11]

The effect of age on post-thrombolysis hemorrhage has long been debated. Advancing age is generally associated with reduced vascular elasticity, increased intima–media thickness, and impaired vascular repair capacity, all of which may increase the susceptibility of the cerebral microcirculation to pressure-related injury.[12] In older patients, collateral vascular compensation is often reduced, and ischemic damage may be more advanced before arterial recanalization occurs, further increasing tissue vulnerability to hemorrhagic transformation.[13] In the present study, although the mean age was higher in patients with hemorrhage than in those without, this difference did not reach statistical significance.

Sex does not appear to be a direct determinant of hemorrhage following alteplase administration; however, hormonal status, overall cerebrovascular condition, and sex-related differences in the prevalence of underlying comorbidities may influence pathophysiological responses.[14] For example, in postmenopausal women, reduced estrogen levels may lead to decreased endothelial nitric oxide availability and increased oxidative stress, thereby enhancing vascular vulnerability. In the present study, no statistically significant association was observed between sex and the occurrence of intracerebral hemorrhage.

From a temporal perspective, a longer interval between symptom onset and alteplase administration is likely associated with more extensive tissue necrosis. This, in turn, may structurally weaken capillary and arteriolar walls, so that the restoration of blood flow can precipitate more severe reperfusion injury.[15] Under such conditions, even blood pressure levels within the upper-normal range may be sufficient to promote hemorrhage. In the present study, although the frequency of intracerebral hemorrhage increased as the time from symptom onset to thrombolysis became longer, this relationship was not statistically significant.

Surgical interventions performed on patients with hemorrhage reflect both the severity and anatomical location of the bleeding. Hematoma evacuation becomes necessary when the hemorrhage volume produces substantial mass effect or structural displacement within the brain, particularly in the setting of rising intracranial pressure and impending life-threatening deterioration.[16] Decompressive craniectomy is typically reserved for cases of severe cerebral edema and refractory intracranial hypertension despite medical treatment.[17] Placement of a shunt or external ventricular drain is generally indicated in the setting of acute obstructive hydrocephalus, which may occur following intraventricular extension of the hemorrhage.[18]

Pharmacological treatment with antifibrinolytic agents is used selectively to directly inhibit fibrinolytic activity, reduce

ongoing bleeding, and stabilize clot formation.[19] The administration of such agents, particularly tranexamic acid, may benefit patients whose hemostatic function remains impaired because of the residual effects of alteplase.[20] However, the routine use of these medications has not yet achieved universal consensus, and treatment decisions should be individualized according to each patient's clinical condition and risk profile.[21]

From a preventive standpoint, strict blood pressure control before, during, and after alteplase administration is one of the most important strategies for reducing hemorrhagic complications. Protocols aimed at maintaining systolic blood pressure below 180 mmHg and diastolic blood pressure below 105 mmHg may reduce the likelihood of intracerebral hemorrhage.[22] Continuous monitoring, early detection of blood pressure elevation, and prompt antihypertensive intervention are also critical components of post-thrombolysis care.[23]

The findings of the present study align with a substantial portion of the existing literature and underscore that the risk of intracerebral hemorrhage following alteplase is determined by the interaction of hemodynamic, pathological, and therapeutic factors. These observations highlight the importance of individualized patient assessment, rigorous blood pressure monitoring, careful consideration of treatment timing, and rational selection of surgical or pharmacological interventions when hemorrhagic complications occur.[24]

Conclusion

This study demonstrated that patients who developed intracerebral hemorrhage following thrombolysis exhibited higher diastolic blood pressure during the first 24 hours compared to those without hemorrhage, while systolic blood pressure did not differ significantly between the two groups overall. Surgical and pharmacological interventions were selected according to hemorrhage severity, location, and each patient's clinical status. These findings emphasize the importance of strict blood pressure control and individualized therapeutic decision-making in preventing and managing thrombolysis-related complications.

References:

1. The writing group of clinical practice guideline for stroke. Clinical practice guideline for stroke. Seoul: Clinical Research Center for Stroke; 2009.
2. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2018; 71: e127–e248. doi: 10.1016/j.jacc.2017.11.006.
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018; 36: 1953–2041. doi: 10.1097/HJH.0000000000001940.
4. Kim HC, Ihm SH, Kim GH, Kim JH, Kim KI, Lee HY, et al. 2018 Korean Society of Hypertension guidelines for the management of hypertension: part I-epidemiology of hypertension. Clin Hypertens. 2019; 25: 16. doi: 10.1186/s40885-019-0121-0.
5. Lee HY, Shin J, Kim GH, Park S, Ihm SH, Kim HC, et al. 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension. Clin Hypertens. 2019; 25: 20. doi: 10.1186/s40885-019-0124-x.
6. Kim KI, Ihm SH, Kim GH, Kim HC, Kim JH, Lee HY, et al. 2018 Korean Society of Hypertension guidelines for the management of hypertension: part III-hypertension in special situations. Clin Hypertens. 2019; 25: 19. doi: 10.1186/s40885-019-0123-y.
7. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015; 46: 3020–3035. doi: 10.1161/STR.0000000000000074.
8. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. Int J Stroke. 2016; 11: 134–147. doi: 10.1177/1747493015609778.
9. Ko SB, Park HK, Kim BM, Heo JH, Rha JH, Kwon SU, et al. 2019 update of the Korean clinical practice guidelines of stroke for endovascular recanalization therapy in patients with acute ischemic stroke. J Stroke. 2019; 21: 231–240. doi: 10.5853/jos.2019.00024.
10. Mazighi M, Richard S, Lapergue B, Sibon I, Gory B, Berge J, et al. Safety and efficacy of intensive blood pressure lowering after successful endovascular therapy in acute ischaemic stroke (BP-TARGET): a multicentre, open-label, randomised controlled trial. Lancet Neurol. 2021; 20: 265–274. doi: 10.1016/S1474-4422(20)30483-X.
11. Yang P, Song L, Zhang Y, Zhang X, Chen X, Li Y, et al. Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial. Lancet. 2022; 400: 1585–1596. doi: 10.1016/S0140-6736(22)01882-7.
12. Mistry EA, Hart KW, Davis LT, Gao Y, Prestigiacomo CJ, Mittal S, et al. Blood pressure management after endovascular therapy for acute ischemic stroke: the BEST-II randomized clinical trial. JAMA. 2023; 330: 821–831. doi: 10.1001/jama.2023.14330.
13. Nam HS, Kim YD, Heo J, Lee H, Jung JW, Choi JK, et al. Intensive vs conventional blood pressure lowering after endovascular thrombectomy in acute ischemic stroke: the OPTIMAL-BP randomized clinical trial. JAMA. 2023; 330: 832–842. doi: 10.1001/jama.2023.14590.
14. US Agency for Health Care Policy and Research. Acute pain management: operative or medical procedures and trauma. Clinical practice guideline no. 1. AHCPR publication no. 92-0032. Rockville, MD: US Department of Health and Human Services, Public Health Service; 1992.
15. Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care. 1986; 2: 53–63. doi: 10.1017/s0266462300002774.
16. Kim JE, Ko SB, Kang HS, Seo DH, Park SQ, Sheen SH, et al. Clinical practice guidelines for the medical and surgical management of primary intracerebral hemorrhage in Korea. J Korean Neurosurg Soc. 2014; 56:175–187. doi: 10.3340/jkns.2014.56.3.175.
17. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, et al. Effects of antihypertensive treatment after acute stroke in the continue or stop post-stroke antihypertensives collaborative study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol. 2010; 9: 767–775. doi: 10.1016/S1474-4422(10)70163-0.
18. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet. 2011; 377: 741–750. doi: 10.1016/S0140-6736(11)60104-9.

19. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014; 311: 479–489. doi: 10.1001/jama.2013.282543.
20. Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, et al. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. Int J Stroke. 2015;10:745–751. doi: 10.1111/ijs.12446.
21. Lee M, Ovbiagele B, Hong KS, Wu YL, Lee JE, Rao NM, et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. Stroke. 2015; 46: 1883–1889. doi: 10.1161/STROKEAHA.115.009552.
22. Zhao R, Liu FD, Wang S, Peng JL, Tao XX, Zheng B, et al. Blood pressure reduction in the acute phase of an ischemic stroke does not improve short- or long-term dependency or mortality: a meta-analysis of current literature. Medicine (Baltimore) 2015; 94: e896. doi: 10.1097/MD.0000000000000896.
23. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995; 333: 1581–1588. doi: 10.1056/NEJM199512143332401.
24. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359: 1317–1329. doi: 10.1056/NEJMoa0804656.