의학석사 학위논문

단일 피질하 경색의 분류와 위치에 따른 치료적 혈압 상승 요법의 효과 비교

Effect of induced hypertension therapy according to different mechanism of Single Subcortical Infarction

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이 논문을 의학석사 학위 논문으로 제출함

2023 년 8 월

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ABSTRACT

Background and Objective: Early neurological deterioration (END) is associated with poor outcome in single subcortical infarction (SSI). Induced hypertension therapy (IHT) demonstrated efficacy in treating END in the non-cardioembolic stroke. Considering the diverse pathomechanisms within the SSI group, this study aimed to investigate the effectiveness of IHT in treating END specifically in SSI cases. We hypothesized that the response to IHT may vary depending on the underlying mechanism of SSI.

Methods: We conducted a study involving patients with SSI who experienced END and received IHT. SSI was classified as proximal (pSSI; infarction extended to the basis of basal ganglia or basis pontis), distal (dSSI) and SSI with parental artery disease (SSIPAD; with stenosis at parental artery disease < 50%). END was defined as worsening of National Institution of Health Stroke Scale (NIHSS) score more than 2 points, 1 point in motor score or the emergence of any new neurological symptoms as indicated by the NIHSS score. IHT was performed via intravenous phenylephrine infusion targeting 10-20% elevation of baseline systolic blood pressure. The response to IHT was defined as reduction of more than 2 points in the total NIHSS score, any observed decrease in the motor score or complete disappearance of newly developed neurological symptoms documented during the episode of END. Characteristic were compared between responder and non-responder. Factors associated with response of induced hypertension were investigated.

Results: among 1224 cases with SSI, 96 patients (49 responder and 47 non responder) were enrolled. There were no significant differences between responders and non-responders except, Hba1c level (responder: 6.2 [5.5-7.25] vs. non-responder: 6.1 [5.4-7.6]; p-value < 0.001) and BP variability (responder: 12.09 [8.71-16.28] vs. non-responder: 13.03 [9.51-15.69]; p-value < 0.001). In the imaging data, the only notable difference between responders and non-responders was the type of SSI. Among responders, pSSI was the most common type (61.2%) whereas, among non-responder,

SSIPAD was most common (42.6%). Multivariable analysis revealed that pSSI (reference = dSSI; adjusted Odds Ratio = 24.7; 95% confidence interval 4.84 - 126.7; p-value < 0.001), Fazekas scale of deep white matter (reference = Fazekas scale 0; Fazekas scale 2 adjusted Odds Ratio = 0.15; 95% confidence interval 0.03.- 0.69; p-value = 0.021) and blood urea nitrogen (adjusted Odds Ratio = 1.11; 95% confidence interval 1.02 – 1.22; p-value = 0.019) were significantly associated with the response to IHT.

Conclusion: Our analysis revealed that among patients with SSI and END, the response to IHT varied depending on the type of SSI. Particularly, our findings indicated that patients with pSSI demonstrated a better response to IHT compared to those with dSSI.

Keywords: induced hypertension therapy, early neurologic deterioration, single subcortical infarction

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INTRODUCTION

Early neurologic deterioration (END), characterized by a worsening of neurological symptoms resulting from various causes, significantly impacts both short-term and long-term functional outcomes. END affects approximately one third of patients who have experienced acute ischemic stroke.[1,2] Moreover, studies have shown that END is also prevalent in patients with single subcortical infarction (SSI), with rates ranging from 13% to 41%. Notably, END has been consistently associated with a poor prognosis for individuals affected by SSI.[3]

In cases of large artery atherosclerosis (LAA) or cardioembolism (CE), where endovascular thrombectomy (EVT) or angioplasty may be viable treatment options for END, the situation is more challenging for SSI patients. The available treatment options for managing the END of single subcortical infarction are limited, and there is an absence of established guidelines specifically tailored to address END in SSI cases.

The utilization of induced hypertension therapy (IHT), which involves the administration of phenylephrine, has emerged as a promising and well-tolerated treatment modality for non-cardioembolic ischemic stroke patients who experience early neurologic deterioration while undergoing hospitalization.[4] By increasing perfusion through collaterals, IHT offers a means of safeguarding neuronal function in the penumbra.[4] Recent investigations have revealed that even in cases of small vessel disease, such as single subcortical infarction, the penumbra—a concept traditionally associated with larger vessel occlusions—may also manifest.[5]

Single subcortical infarction can be classified based on the size and location of the ischemic core lesion, each exhibiting distinct pathomechanisms and characteristics of penumbra tissue.[6] As the number of evidence continues to grow, it becomes apparent that the intricate branching patterns of the perforator vessels plays a significant role in influencing the infarct core within SSI.[7] This understanding is further supported by the fact that the length and location of the infarcted lesion served as predictive factors for END.[8,9] The heterogeneous nature of SSI, with its varied subtypes

demonstrating diverse prognoses and pathomechanisms, we hypothesize that the response to induced hypertension therapy may differ according to the specific types of single subcortical infarction.

METHODS

Participants and clinical data

We conducted a retrospective review of patients who were admitted to the Stroke Center of Asan Medical Center (AMC) in Seoul between January 2017 and May 2022. The inclusion criteria for our analysis were as follows: 1) patients aged 18 years or older who had been diagnosed with ischemic stroke, 2) individuals with a discernible single subcortical lesion identified through diffusion-weighted imaging that corresponded to the observed neurological deficit, 3) patients who experienced END during their hospitalization, and 4) individuals who underwent IHT. We excluded patients with 1) insufficient imaging or clinical data, as well as 2) those with confirmed greater than 50% stenosis of the parent artery based on magnetic resonance angiography (MRA).

To gather relevant data, we collected demographics, vascular risk factors, and vital signs including blood pressure measurements, from the electronic medical records and stroke database. Risk factors were defined as hypertension (previously prescribed antihypertensive drugs or systolic blood pressure > 140 mmHg), diabetes mellitus (previously prescribed glucose-lowering agents or hemoglobin A1c >= 6.5%), hyperlipidemia (previously prescribed lipid-lowering agents or total cholesterol >= 240 mg/dL or one or more of the followings : fasting low density lipoprotein >= 160 mg/dL, triglyceride >= 200mg/dL or high density lipoprotein < 40 mg/dL), smoking, and previous history of cerebral infarction or transient ischemic attack. Additionally, the severity of neurological deficits was assessed using the National Institute of Health Stroke Scale (NIHSS) scores at admission and was followed up regularly after admission by a skilled neurologist in accordance with the established protocols of our center. The institutional review boards of Asan Medical Center approved the study (IRB no. 2022-0830), and due to the retrospective nature of this analysis, written informed consent was waived.

Imaging protocol and analysis

In this study, we conducted an analysis of the initial brain MRI images acquired during hospitalization. Various imaging modalities were utilized, including diffusion-weighted image (DWI), fluid attenuated inversion recovery image (FLAIR), gradient echo image (GRE), brain perfusion image, and MR angiography. The image slices were obtained at intervals of 3 mm or 5 mm, and for MR angiography, both time-of-flight (TOF) and contrast-enhanced images were examined.

The degree of white matter change was assessed by dividing it into deep white matter and periventricular white matter and classifying it using the Fazekas scale on the FLAIR images. Additionally, we counted lacunes (lesions with a signal intensity equivalent to cerebrospinal fluid, with a size of 3 mm or more and high signal intensity along the border in FLAIR images) and microbleeds (lesions with low signal intensity measuring less than 10 mm in GRE images). Perfusion abnormalities were evaluated using perfusion-weighted images, where an increase in signal intensity in the time-to-peak (TTP) map indicated abnormal perfusion. Researchers also assessed diffusion-perfusion mismatch by comparing the DWI and TTP map.

Type of Single Subcortical Infarction

Single Subcortical Infarction (SSI) was defined as infarction in the perforator artery territory (basal ganglia, corona radiata, internal capsule, medulla oblongata, pons and midbrain) in the diffusion weighted image at the hospitalization.[10]

Through MR angiography, cases with parent artery stenosis below 50% were categorized as Single Subcortical Infarction with Parent Artery Disease (SSIPAD). Cerebral infarction without parent artery disease was further classified into Proximal Single Subcortical Infarction (pSSI) and Distal Single Subcortical Infarction (dSSI), based on whether the infarction reached the base of the parent artery. Specifically, in the anterior circulation, pSSI was defined as the infarction extending to

the lowest part of the basal ganglia.[10,11] In the posterior circulation, pSSI was defined as the infarction adjacent to the basilar artery.

Early Neurological Deterioration

END was defined as an increase of more than 2 points in the total NIHSS score, an increase in the NIHSS motor score, or the emergence of any new neurological symptoms as indicated by the NIHSS score. Whenever END was observed, the underlying cause was assessed. In situations where there was evidence of stroke progression, the potential implementation of IHT was considered based on the patient's clinical condition. Patients with IHT was not considered in patients with history of significant cardiac arrhythmia such as ventricular arrhythmia, atrial fibrillation, atrial flutter and high degree of sinus block, history of significant coronary artery disease, history of significant congestive heart failure, hypertrophic cardiomyopathy, pregnancy, use of MAO inhibitor and initial systolic blood pressure above 180 mmHg.

In the case of initiating the IHT, we recorded all blood pressure measurements taken prior to the initiation of therapeutic induced hypertension after admission. To assess blood pressure variability, we calculated the standard deviation of these recorded values. Additionally, we measured various laboratory parameters, including hemoglobin, white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glycated hemoglobin (HbA1c).

Method of Induced Hypertension Therapy

IHT was administered to patients through continuous intravenous phenylephrine infusion, which involved elevating blood pressure by approximately 10% to 20% above the baseline level. A solution of 10mg 1% phenylephrine was mixed with 250mL of normal saline. The time interval between the

onset of END and the initiation of IHT was recorded. The initial dose of phenylephrine was 0.5 mcg/kg/min, with a maximum dose of 3.0 mcg/kg/min. To achieve the target blood pressure, the dose was increased by 0.2 mcg/kg/min every 20 minutes while closely monitoring the blood pressure response at the same interval. Once the target blood pressure was reached, blood pressure was monitored for 2 hours. If the measured blood pressure deviated from the target, the dose of phenylephrine was adjusted every 20 minutes, either increased or decreased, to maintain the target blood pressure.

The response to therapeutic induced hypertension was assessed based on specific criteria. This included a reduction of more than 2 points in the total National Institutes of Health Stroke Scale (NIHSS) score, any observed decrease in the motor score or complete disappearance of newly developed neurological symptoms documented during the episode of END.

Statistical analysis

The study aimed to compare the characteristics of responders and non-responders to therapeutic induced hypertension. Continuous variables were summarized using the median (interquartile range) for non-normally distributed data and the mean for normally distributed data. Categorical variables were presented as absolute numbers and percentages. The Mann-Whitney U test and t-test were employed to compare continuous variables with non-normal and normal distributions, respectively. The fisher's exact test or chi-square test was used for comparing categorical variables.

Multivariable logistic regression analysis was conducted to identify factors associated with the response to IHT. Parameters that were found to be significant in the univariate analysis at a P-value below 0.15 or were known to be relevant based on previous studies were included. A backward elimination approach was employed during regression analysis. All statistical tests were two-tailed, and a significance level of $P < 0.05$ was considered statistically significant. The statistical analysis

was performed using R 4.3.1 software.

RESULTS

Baseline characteristics

Out of the 6959 patients enrolled in the Asan Stroke registry between January 2017 and May 2022, a total of 1156 cases were classified as Small Vessel Disease (SVD) according to the TOAST classification. Among these 1156 cases, IHT was conducted in 117 cases. However, 21 cases were excluded from the analysis as they did not meet the inclusion criteria, such as cases where early neurologic deterioration (END) was not documented, or END was documented before admission. After excluding these cases, a final sample of 96 cases was included in the analysis (Figure 1).

In our study, 61.5% (59) of the participants were male. Among the responders, 59.2% (29) were male, while among the non-responders, 63.8% (30) were male (p-value = 0.64). The mean age of the participants was 64.7 ± 12.9 years. In the responder group, the mean age was 64.2 ± 13.16 years, while in the non-responder group, it was 65.28 ± 10.53 years (p-value = 0.6611) (Table 1).

The prevalence of hypertension in the patient population was 65.6% (63), with 59.2% (29) among the responders and 72.3% (34) among the non-responders (p-value = 0.175). Diabetes mellitus was present in 39.6% (38) of the patients, with 36.7% (18) among the responders and 42.6% (20) among the non-responders (p-value = 0.56). Hyperlipidemia was found in 40.6% (39) of the patients, with 36.7% (18) among the responders and 44.7% (21) among the non-responders (p-value = 0.428) (Table 1).

Regarding the medical history, a previous ischemic stroke was reported by 14.6% (14) of the patients, with 12.2% (6) among the responders and 17.0% (8) among the non-responders (p-value = 0.507). A history of previous transient ischemic attack was found in 3.1% (3) of the patients, with 2.0% (1) among the responders and 4.3% (2) among the non-responders (p-value = 0.613). The current smoking status was observed in 43.8% (42) of the patients, with 49.0% (24) among the responders and 38.3% (18) among the non-responders (p-value = 0.292). A history of previous antiplatelet

therapy was reported by 6.2% (6) of the patients, with 4.1% (2) among the responders and 8.5% (4) among the non-responders (p-value = 0.461) (Table 1).

The median admission NIHSS score was 5.0 (3.0-7.0) points, with 5.0 (4.0-7.0) points among the responders and 5.0 (2.25-7.0) points among the non-responders (p-value = 0.5009). The median END NIHSS score was 7.0 (3.0-7.0) points, with 7.0 (6.0-9.0) points among the responders and 7.0 (4.5-8.0) points among the non-responders (p-value = 0.1366) (Table 1).

The median time delay between END and the initiation of therapeutic induced hypertension was 3.75 (0.5-7.0) hours. Among the responders, the median time delay was 12.09 (8.71-16.28) hours, while among the non-responders, it was 13.03 (9.51-15.69) hours (p-value = 0.4796). Blood pressure variability showed a significant difference between responders and non-responders, with values of 12.09 (8.71-16.28) and 13.03 (9.51-15.69), respectively (p-value < 0.001) (Table 1).

Regarding laboratory findings, no statistical differences were observed except for HbA1c levels. The median HbA1c was 6.1 (5.4-7.6) among the responders and 6.2 (5.5-7.25) among the non-responders (p-value < 0.001) (Table 2).

Image data

Our analysis revealed that there were no significant differences observed between responders and non-responders in terms of periventricular and deep white matter hyperintensity, lacunes, microbleeds (Table 3).

Furthermore, our study did not identify any correlation between the location of the infarction (specifically, whether it occurred in the anterior or posterior circulation) and the response to therapeutic induced hypertension (Table 3). However, when examining the types of single subcortical infarction, a notable difference was observed (Table 3). Among the responders, 8.2% (4) had dSSI, 61.2% (30) had pSSI, and 30.6% (15) had SSIPAD. In contrast, among the non-responders, 38.3% (18) had dSSI, 19.1% (9) had pSSI, and 42.6% (20) had SSIPAD. This difference was found to be statistically significant (p-value<0.001).

Subgroup analysis

In our study, we conducted a further investigation to examine the potential correlation between diffusion-perfusion mismatch and the response to IHT. Out of the 97 patients included in the study, a total of 51 patients underwent MR imaging with perfusion weighted imaging during hospitalization (Table 4). Among these patients, 52.2% (12) were classified as non-responders, while 39.3% (11) were categorized as responders. Upon analyzing the data, we did not observe any statistically significant findings suggesting a correlation between diffusion-perfusion mismatch and the response to IHT (Table 4).

Multivariable logistic regression

we considered several factors that were known to be relevant in the response to therapeutic induced hypertension and early neurologic deterioration (END). These factors included age, sex, the time duration between END and induced hypertension. And END NIHSS score, blood pressure variability, types of single subcortical infarction (dSSI vs. pSSI), deep white matter (DWM) Fazekas scale, platelet count, blood urea nitrogen (BUN), glycated hemoglobin (HbA1c), which were identified as significant parameters in the univariate analysis at a P-value < 0.15 level were included in the regression.

To determine the independent associations between these factors and the response to therapeutic induced hypertension, we performed a multivariable logistic regression analysis with backward elimination. The results revealed that the type of single subcortical infarction (adjusted odds ratio 23.0, 95% confidence interval 5.66-125), DWM Fazekas scale (adjusted odds ratio 0.15, 95% confidence interval 0.03-0.69), and BUN (adjusted odds ratio 1.11, 95% confidence interval 1.02-1.22) were significantly associated with the response to therapeutic induced hypertension.

DISCUSSION

Among 97 patients included in the study, approximately half of patients (51%) exhibited response to the IHT. Univariate analysis revealed that only two factors, BP variability and HbA1c level showed significant difference between responders and non-responders. However, in the multivariate analysis, several factors emerged as significant predictors of response to IHT. These factors include the type of single subcortical infarction (SSI), particularly between distal SSI (dSSI) and proximal SSI (pSSI), as well as the presence of deep white matter leukoaraiosis and blood urea nitrogen level. However, the clinical significance of this difference in BUN levels remains uncertain.

The effectiveness of IHT in acute non-cardioembolic infarction or infarction with vessel stenosis has been increasingly reported in previous studies.[4,12,13] Studies have shown that in large artery disease (LAD), END is associated with perfusion impairment.[12] Similarly, diffusion-perfusion mismatch has been detected in transient ischemic attack (TIA) or END of SSI cases.[5] Diffusion-perfusion mismatch in SSI has been identified as a reliable predictor of END.[3] The mechanism of END in SSI, which occurs in territories lacking collateral supply from perforator arteries, is related to an increase in infarction volume or diffusion-perfusion mismatch.[3] It has been observed that dSSI has a lower incidence of END and better clinical outcomes compared to pSSI.[10,14,15] Similarly, the presence of parental artery disease has been identified as a predictor of END.[16]

However, our study demonstrated that pSSI showed a better response to therapeutic induced hypertension, and there was a similar trend observed in cases of SSI with parental artery disease, although statistical significance was not achieved. SSI with parental artery stenosis tends to have a larger penumbra compared to dSSI, as the infarction is limited to the distal branch of the perforator artery, which may contribute to the better response to IHT. The size and location pattern of pSSI can vary depending on the branching pattern of the perforating artery, and pSSI often presents with a higher prevalence of atherosclerosis indicators. Like the cases of SSIPAD, pSSI involves the proximal part of the perforator branch, leading to more pronounced diffusion-perfusion mismatch compared to

dSSI, and consequently exhibiting a better response to therapeutic induced hypertension, which promotes brain perfusion.

Theoretically, SSIPAD is characterized by a vascular lesion in the most proximal part and is expected to have a larger penumbra compared to pSSI. However, our study did not find statistical significance in the response to IHT among SSIPAD cases. This lack of statistical significance in the response to therapeutic induced hypertension among SSIPAD cases may be attributed to the presence of vessel stenosis, even though the degree of stenosis is not severe. While vessel stenosis may not be highly significant in terms of severity, it can still impact blood flow dynamics. The presence of stenosis can lead to increased blood velocity and turbulence, potentially resulting in lower blood pressure at the site of the perforating artery.[17] The decrease in blood pressure may interfere with the intended effects of therapeutic induced hypertension in these cases.

White matter hyperintensity, known as an indicator of small vessel disease, has produced various results in studies investigating its relationship with END.[18,19] Our study revealed a negative impact of a high Fazekas scale of the deep white matter, on the response to IHT. This finding aligns with our conclusion as dSSI, which tends to exhibit a high prevalence of small vessel disease indicators, showed a poor response to IHT. It is worth noting that only the Fazekas scale of deep white matter, not the periventricular white matter, demonstrated this negative correlation with IHT. This observation highlights the distinct pathogenic mechanisms between periventricular and deep white matter hyperintensities.[20] Periventricular white matter hyperintensities are known to be associated with hemodynamic factors, while deep white matter hyperintensities are more closely related to small vessel disease.[20]

White matter hyperintensities and cerebral autoregulation, which regulates cerebral blood flow through the interaction of myogenic, neurogenic, and metabolic mechanism have been established to have a close relationship, with bidirectional interaction.[21] Previous studies have shown that in the state of normal cerebral autoregulation, there is endothelium-dependent vasodilation observed during hypertensive state.[22] However, normal vasodilation response to IHT may be disrupted in the presence

of severe white matter hyperintensities. This can result in a less effective perfusion increase in the penumbra area. Dysfunction in autoregulation associated with white matter hyperintensities may therefore contribute to poor response to IHT.

LIMITATION

Our study has several limitations. Firstly, our analysis was conducted at a single center, which may limit the generalizability of our findings to other medical institutions. Secondly, the number of cases included in our study was relatively limited. However, it is worth considering that the number of cases enrolled in previous randomized controlled trials investigating IHT in non-cardioembolic stroke patients was around 150. In this context, the case number in our study was deemed sufficient for comparing the response to IHT based on the specific types of SSI. Thirdly, due to the quality of the perfusion-weighted images, we were unable to conduct a quantitative analysis of the diffusion-perfusion mismatch.

CONCLUSION

The findings from our study revealed that despite the higher risk of early neurologic deterioration (END) observed in patients with proximal single subcortical infarction (pSSI) and single subcortical infarction with parent artery disease (SSIPAD), pSSI exhibited a more favorable response to IHT when compared to distal single subcortical infarction (dSSI). Furthermore, SSIPAD also demonstrated a similar trend. These results suggest the need for aggressive screening and intervention strategies specifically targeted towards cases of pSSI.

Figure 1. Flowchart of the inclusion process

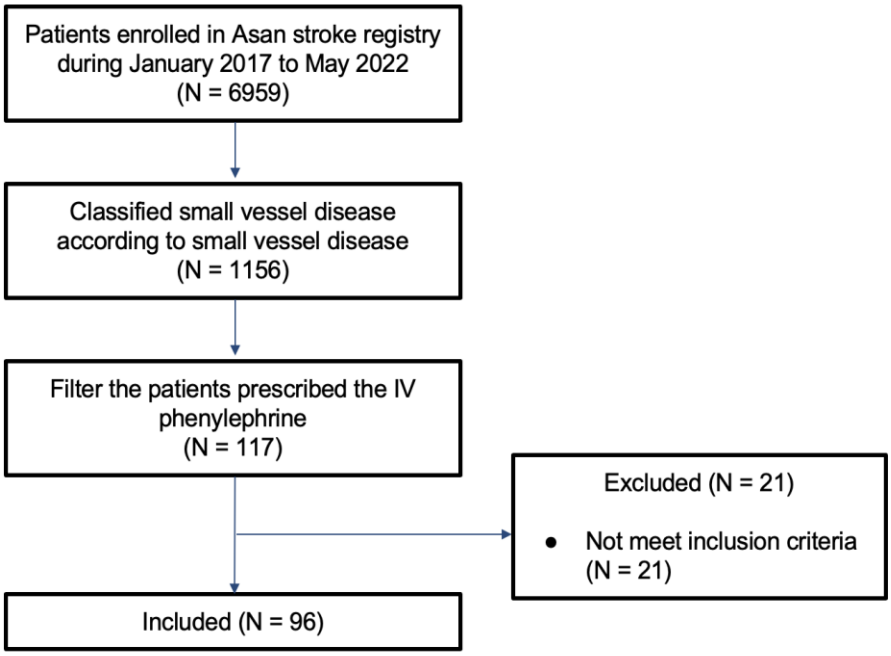

Table 1. Baseline characteristic

Baseline Characteristic	Non-responder (N = 47)	Responder (N = 49)	p-value
Age, mean +- SD, y	65.28 +- 10.53	64.2 +- 13.16	0.661
Male, N (%)	30 (63.8)	29 (59.2)	0.797
Hypertension, N (%)	34 (72.3)	29 (59.2)	0.175
Diabetes Mellitus, N (%)	20 (42.6)	18 (36.7)	0.560
Hyperlipidemia, N (%)	21 (44.7)	18 (36.7)	0.428
History of stroke, N (%)	8 (17.0)	6 (12.2)	0.507
History of transient ischemic attack, N (%)	2 (4.3)	1 (2.0)	0.613
Smoking, N (%)	18 (38.3)	24 (49.0)	0.292
Previous Antiplatelet treatment, N (%)	4 (8.5)	2 (4.1)	0.431
Initial Systolic Blood Pressure (BP), mean +- SD, mmHg	154.81 +- 16.22	151.92 +- 20.85	0.452
BP variability, median (IQR), mmHg	13.03 (9.51-15.69)	12.09 (8.71-16.28)	< 0.001
Admission NIHSS score, median (IQR)	5 (2.5-7.0)	5 (4.0-7.0)	0.501
Early Neurological Deterioration (END) NIHSS score, median (IQR)	7.0 (4.5-8.0)	7.0 (6.0-9.0)	0.137
Time duration between END and induced hypertension, median (IQR), hr	3.75 (0.5-7.0)	2 (1.0-6.0)	0.480

Table 2. Laboratory findings

Laboratory Findings	Non-responder (N = 47)	Responder (N =49)	p-value
Hemoglobin, mean +- SD, g/dL	14.14 +- 1.64	14.16 +- 1.76	0.948
Leukocyte, mean +- SD, 10^3	7.53 +- 2.13	7.72 +-1.73	0.631
Platelet count, mean +- SD, 10^3	231.83 +- 49.83	250.2 +- 64.14	0.121
Erythrocyte sedimentation rate (ESR), median (IQR), mm/hr	11.0 (5.0-20.0)	15.0 (5.0-24.0)	0.432
C-reactive Protein (CRP), median (IQR), mg/dL	0.1 (0.1-0.160)	0.1 (0.1-0.19)	0.964
Blood Urea Nitrogen (BUN), median (IQR), mg/dL	15.0 (11.0-16.5)	15.0 (13.0-20.0)	0.128
Creatinine, median (IQR), mg/dL	0.83 (0.725-0.925)	0.79 (0.72-0.92)	0.942
Total cholesterol, mean +- SD, mg/dL	188.47 +- 35.88	184.86 +- 41.38	0.649
Low-density Lipoprotein, mean +- SD, mg/dL	125.44 +- 32.2	119.71 +- 40.34	0.451
High-density Lipoprotein, mean +- SD, mg/dL	53.46 +- 14.52	50.18 +- 12.57	0.242
Triglyceride, median (IQR), mg/dL	125 (88-191)	148 (104-203)	0.173
Glycated hemoglobin (HbA1c), median (IQR), %	6.2 (5.5-7.25)	6.1 (5.4-7.6)	<0.001

Table 3. Image data

Image Data	Non-responder (N = 47)	Responder (N = 49)	p-value
Posterior Circulation, N (%)	17 (36.2)	23 (46.9)	0.285
Type			
dSSI, N (%)	18 (38.3)	4 (8.2)	
pSSI, N (%)	9 (19.1)	30 (61.2)	
SSIPAD, N (%)	20 (42.6)	15 (30.6)	< 0.001
Leukoaraiosis			
Fazekas scale (periventricular white matter)			
0, N (%)	18 (38.3)	25 (51.0)	
1, N (%)	24 (51.1)	22 (44.9)	
2, N (%)	4 (8.5)	2 (4.1)	
3, N (%)	1 (2.1)	0	0.420
Fazekas scale (deep white matter)			
0, N (%)	20 (42.6)	30 (61.2)	
1, N (%)	17 (36.2)	16 (32.7)	
2, N (%)	9 (19.1)	3 (6.1)	
3, N (%)	1 (2.1)	0	0.083

Microbleed			
0, N (%)	42 (91.3)	39 (83.0)	
1, N (%)	1 (2.2)	4 (8.5)	
2, N (%)	0 (0)	2 (4.3)	
>= 3, N (%)	3 (6.5)	2 (4.3)	0.290
Lacunes			
0, N (%)	32 (68.1)	37 (75.5)	
1, N (%)	9 (19.1)	7 (14.3)	
2, N (%)	3 (6.4)	3 (6.1)	
>= 3, N (%)	3 (6.4)	2 (4.0)	0.917

Table 4. Subgroup Analysis

	Non-responder (N = 23)	Responder (N=28)	p-value
Diffusion-Perfusion mismatch, N (%)	12 (52.2)	11 (39.3)	0.357

Table 5. Multivariable logistic regression

	Univariate analysis		Multivariate analysis (Backward Elimination)	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	0.99 (0.96-1.03)	0.657		
Sex	1.22 (0.53-2.79)	0.64		
Time duration between END and induced hypertension	0.98 (0.90-1.05)	0.544		
END NIHSS score	1.13 (0.97-1.35)	0.13		
BP variability	0.99 (0.93-1.06)	0.83		
Type				
dSSI	reference		reference	
pSSI	15.0 (4.38-63.3)	< 0.001	23.0 (5.66-125)	< 0.001
SSIPAD	3.38 (1.01-13.6)	0.061	3.66 (0.95-17.2)	0.073
Deep white matter Fazekas scale				
0	reference		reference	
1	0.63 (0.26-1.52)	0.303	0.49 (0.14-1.53)	0.225
2	0.22 (0.05-8.48)	0.038	0.15 (0.03-0.69)	0.021
>= 3	NA	0.991	NA	0.990
Platelet count	1.006 (0.99-1.01)	0.12		
BUN	1.07 (1.00-1.16)	0.08	1.11 (1.02-1.22)	0.019
HbA1c	0.88 (0.68-1.12)	0.31		

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국문 요약

배경: 조기 신경학적 악화(Early neurological deterioration)는 단일 피질하 경색(Single Subcortical Infarction, SSI)에서 불량한 예후와 연관이 있는 것으로 알려져 있다. 치료적 혈압 상승 요법은 조기 신경학적 악화를 보이는 뇌경색 환자에게서 하나의 치료 대안으로 제시되고 있다.

목적: 단일 피질하 경색의 경우 다양한 병태생리를 가지고 있는 것을 고려하여 피질하 경색의 환자에게서 치료적 혈압 상승 요법의 반응에 대해서 연구를 진행하였다. 우리는 이번 연구에서 단일 피질하 경색의 기전에 따라 치료적 혈압 상승 요법에 대한 반응에 차이를 보일 것으로 가정하였다.

방법: 입원 도중 조기 신경학적 악화가 확인되어 치료적 혈압 상승 요법을 시행한 단일 피질하 경색 환자를 대상으로 연구를 수행하였다. 단일 피질하 경색은 근위 단일 피질하 경색 (proximal SSI; 기저핵의 하단 부분을 침범한 뇌경색 혹은 뇌기저동맥 인접 부위까지 침범한 뇌경색), 원위 단일 피질하 경색 (distal SSI), 그리고 동맥 협착이 확인된 단일 피질하 경색 (SSI with parent artery disease, 동맥에 50% 미만의 협착이 확인되는 경우) 로 분류하였다. 조기 신경학적 악화는 National Institution of Health Stroke Scale(NIHSS) 점수가 2 점 이상, 운동 점수가 1 점 이상 악화되거나 새로운 신경학적 증상이 나타나는 경우로 정의하였다. 치료적 혈압 상승 요법은 기저 수축기 혈압의 10-20% 상승을 목표로 정맥 내 Phenylephrine 주입을 통해 시행하였다. 치료적 혈압 상승 요법에 대한 반응 유무는 총 NIHSS 점수에서 2 점 이상 감소, 운동 점수의 감소 또는 새로 발생한 신경학적 증상의 소실로 정의하였다. 치료적 혈압 상승 요법의 반응의 유무에 따른 특성을 비교하였으며 이와 연관된 요인에 대해서 연구하였다.

결과: 1,224 건의 단일 피질하 경색 중 총 96 명의 환자(반응자 49 명, 무반응자 47 명)가 등록되었다. Hba1c (반응자: 6.2[5.5-7.25] vs. 무반응자: 6.1[5.4-7.6]; p-value < 0.001) 및 혈압 변동성(반응자: 12.09[8.71-16.28] vs. 무반응자: 13.03[9.51-15.69], p-value < 0.001) 에서 치료적 혈압 상승 요법의 반응 유무에 따라 통계학적으로 차이가 확인되었으며 이외 다른 요인에

대해서는 의미 있는 차이가 존재하지 않았다. 영상 검사 결과를 분석하였을 때 반응자와 무반응자 사이에 의미 있는 차이는 단일 피질하 경색의 유형에 따른 차이가 유일하였다. 반응자에서는 pSSI 가 가장 흔한 유형(61.2%)인 반면 무반응자에서는 SSIPAD 가 가장 많았다(42.6%). 다변량 분석 결과 pSSI(기준 = dSSI; Adjusted Odds Ratio = 24.7; 95% 신뢰 구간 4.84 - 126.7; p-value < 0.001), 심부 백질의 Fazekas scale (기준 = Fazekas scale 0; Fazekas scale 2 Adjusted Odds Ratio = 0.15; 95% 신뢰구간 0.03.-0.69; p-value = 0.021) 및 혈액요소질소(Adjusted Odds Ratio = 1.11; 95% 신뢰구간 1.02 – 1.22; p-value = 0.019) 에서 치료적 혈압 상승 요법에 대한 반응과 연관이 있는 것으로 확인되었다.

결론: 조기 신경학적 악화가 동반된 단일 피질하 경색 환자에서 단일 피질하 경색의 기전에 따라 치료적 혈압 상승 요법의 효과에 차이가 확인되었으며 dSSI 와 비교하여 pSSI 에서 치료적 혈압 상승 요법이 효과적이었다.