Role of 24-Hr Blood Pressure Variability as a Target Therapeutic Risk Factor for Poor Functional Outcome of Acute Ischemic Stroke

Nithisha Thatikonda, Vinod Khandait¹, Aditya Shrikhande, Krittika Singh
Undergraduate Medical Student, ¹Department of Medicine, Govt. Medical College Nagpur, MUHS, Nagpur, Maharashtra, India

Abstract

Background and Purpose: The present study aims to evaluate the role of blood pressure variability (BPV) as a target therapeutic risk factor for poor outcome of ischemic stroke by finding the association between the two and by finding the population attributable risk (PAR) of BPV compared to other baseline outcome predictors. Methods: A prospective observational study was conducted at GMCH, Nagpur, India from January to June 2019 in 75 patients diagnosed with acute ischemic stroke. BP was recorded hourly for the first 24 hours of admission and baseline factors were collected along with measurement of stroke severity. BPV was measured by index of average real-time variability (ARV) while discharge outcome was measured by Barthel Index. Results: 36.5% of patients had poor outcome at discharge. A significant association was found between 24-hr ARV of systolic BP and poor outcome (P = 0.002, 95% CI = 2.22-23.5). Five factors were found to be independent outcome predictors on multiple logistic regression (OR, 95% CI): age (1.07, 1.03-1.10), NIHSS score (1.12, 1.04-1.27), on admission SBP (5.12, 4.01-16.23), on admission RBS (2.23, 1.92-6.49) and 24 Hr ARV-SBP (9.65, 3.02-20.1). The PAR of 24 hr ARV-SBP was 23.6%, second only to NIHSS score (26.4%). Conclusions: Reduction in BP variability might have a beneficial impact on the outcome of patients with acute ischemic stroke. There is further scope to explore optimum therapeutic strategies to minimize BPV in the management of acute ischemic stroke.

Keywords: Blood pressure variability, ischemic stroke, outcome predictors, population attributable risk

INTRODUCTION

Although significant achievements have been made in the field of early treatment, management, and secondary prevention of ischemic stroke, a remarkable proportion of patients still experience morbidity and mortality.[1,2] Large number of studies have aimed at identifying the predictors of outcomes in ischemic stroke patients of in order to formulate and improve treatment decisions.[3-5] Since blood pressure (BP) generally undergoes abrupt changes in the acute phase (first 24 hours of onset) of ischemic stroke, BP level at admission has been established as an important independent predictor of stroke outcome.[6-8] Hence, present treatment guidelines were made to target elevated BP.

Data from randomized controlled trials (RCTs) suggest that though BP can be safely reduced after the acute stroke period, there seems to be no indication that doing so is beneficial.[9-11] The Cochrane meta-analysis and guidelines state that optimal BP management in the context of initial stroke treatment remains uncertain.[12]

BP variability (BPV) might serve as an alternative explanation for the lack of evidence and uncertainty of treating elevated BP levels in acute stroke.[13] Current hypertension guidelines predominantly focus on mean casual BP measurements, dismissing BPV as random and merely an obstacle in the estimation of usual BP. Nevertheless, the importance of BPV has been emphasized recently and focus has shifted to “increased BPV” as a risk factor for cardiovascular morbidity and mortality.[14-16] A transient alteration in the autonomic nervous system occurs during the acute phase of ischemic stroke resulting in sympathetic hyperactivity, which is thought to be responsible for this increased BPV.[17,18] Due to impaired cerebrovascular autoregulation after ischemic stroke, BP fluctuation, that is, increased BPV directly affects the brain tissue, leading to the growth of the ischemic lesion resulting in poor functional outcomes.[14,19]

Although several studies have proved that increased BPV results in poor functional outcomes, the potential of BPV as a target therapeutic risk factor has not been studied extensively. Before embarking on RCTs for controlling BPV, its prevalence in the population and its impact on patient outcome have to be studied. Researchers use population attributable risk (PAR) as a tool to prioritize the risk factors that should be modified.
so that effective treatment strategies can be planned. With this background, the current study aims to (i) confirm the association between 24 Hr BPV in acute phase of ischemic stroke and poor functional outcome at the time of discharge and (ii) find the PAR of BPV compared to other known outcome predictors.

**METHODOLOGY**

**Study setup**

A prospective observational study was undertaken from January 2019 to June 2019. Ethical clearance was obtained from the institutional ethics committee. Sample size was calculated with the following formula:

\[
\text{Equation I} = Z_{1-\alpha/2}^2 P (1-P)
\]

\[d^2\]

where \(Z_{1-\alpha/2}\) is standard normal variate which is 1.96 at 5% type I error (\(P < 0.05\)), \(P\) = expected proportion in population based on previous studies, and \(d\) = absolute error which is 5%. A total of 75 patients who were diagnosed with ischemic stroke and admitted to Govt. Medical College and Hospital, Nagpur, India were included in the study. Patients admitted to GMCH within 6 hours of onset of ischemic stroke and confirmed by CT/MRI were included in the study but patients with secondary hemorrhagic transformation were excluded from the study. Written informed consent was obtained from all the patients.

**Data collection**

Data was collected by interview technique with a pre-tested and pre-designed questionnaire which included the sociodemographic variables and the predictor factors that are already known to have an impact on the outcome of ischemic stroke. The factors are described in detail below.

**Assessment of stroke severity**

Stroke severity was assessed by employing the widely used National Institute of Health Stroke Scale (NIHSS), performed by an experienced physician. The NIHSS is composed of 11 items and for each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed up in order to calculate a patient’s total NIHSS score. The maximum possible score is 42, while the minimum score is 0.

**24 Hour ambulatory blood pressure monitoring**

24-hour blood pressure was recorded with a hand-held portable device, CONTEC-ABPM50 (Ambulatory Blood Pressure Monitor) which employs the principle of oscillographic theory. Measurements were obtained hourly for 24 hours during the acute phase of ischemic stroke. Cuff size was selected according to subject’s arm circumference. Based on the results of 24-hr ABPM, systolic and diastolic BPV was calculated using the index of Average Real Variability (ARV) according to the following formula:

\[
\text{Equation II: } \text{ARV} = \frac{1}{N-1} \sum_{k=1}^{n-1} |X_t - BP_k| BP_k
\]

where N denotes the number of valid BP measurements and k is the order of measurements that ranges from 1 to n-1.

ARV is defined as the average of the absolute differences between consecutive BP measurements. Studies have shown it to be a more reliable prognostic indicator compared to other indices like standard deviation (SD) and coefficient of variation (CV) which only reflect the dispersion of BP measurements around the mean.\textsuperscript{[19]} ARV is more sensitive to the individual BP measurement sequence and less sensitive to low sampling frequency.\textsuperscript{[20]}

**Definitions of outcome predictors**

Factors that are already known to have an impact on functional outcome of stroke were collected at baseline and analysed. They are (i) age; (ii) female sex;\textsuperscript{[3-5]} (iii) history of hypertension; (iv) history of diabetes mellitus;\textsuperscript{[4]} (v) hyperlipidemia: total cholesterol (TCH) \(\geq 5.70\) mmol/L and/or triglyceride (TG) \(\geq 2.04\) mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L, low-density lipoprotein cholesterol (LDLC) > 3.2 mmol/L; (vi) active smoking (current smoking vs. never or former smoking); (vii) Regular alcohol consumption (200 ml of wine/champagne or 500 ml of beer or 20 ml of hard liquor at least once per week); (viii) Body mass index;\textsuperscript{[3] (ix) history of atrial fibrillation (AF); (x) history of coronary artery disease (CAD); (xi) On admission random blood glucose levels (RBS) ranging from 70–400 mg/dL. Higher on-admission blood sugar level is proven to be associated with poor outcome;\textsuperscript{[1,21]} (xii) Severity of stroke: stroke severity assessed by NIHSS score at the time of admission and a score > 4 is considered to be a poor outcome predictor;\textsuperscript{[3,5]} (xiii) On-admission systolic BP (SBP): the higher the initial SBP on admission, the worse is the outcome of the patients;\textsuperscript{[6-8]} (xiv) Etiologic subtype of stroke based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification;\textsuperscript{[1,4]} (xv) systolic and diastolic BPV calculated by the index of ARV. Higher ARV values are proven to be associated with poor functional outcomes.\textsuperscript{[19]}

**Poor outcome at discharge measured by Barthel index score**

Poor outcome is defined as functional impairment and dependency on others for daily activities, as measured by Barthel Index (BI) score < 60 at the time of discharge.\textsuperscript{[22-24]} BI is a scale that indicates the ability to perform a selection of activities of daily living. It comprises 10 items (tasks like feeding, bathing, grooming, dressing, bowel and bladder control etc.) with total scores ranging from 0 (worst mobility in activities of daily living/dependent on others) to 100 (full mobility in activities of daily living/independent). The environmental conditions were same for all the patients during hospital stay with no effect on patients’ score. BI scale was applied exclusively by one investigator for all the patients to minimize interrater bias.
Statistical analysis

Continuous variables are reported as means ± SD and categorical variables are reported as percentages. 24 Hr ARV index of both SBP and DBP was calculated with above mentioned formula and association between functional outcome and ARV indices was reported by univariate analysis. Before estimating the PAR of a risk factor, the strength of association between the outcome predictor and functional outcome was determined using odds ratios (ORs) and 95% confidence intervals (CIs) by using univariable logistic regression. For binary risk factors, the reference was selected as the category that describes absence of the risk factor. For categorical risk factors, the reference was selected as the category with the lowest risk of poor functional outcome. Parameters with univariable P values <0.05 were transferred to multiple binary logistic regression analysis with backward selection (α stay = 0.05) to select predictors for further analysis, in order to identify the strongest and mutually independent risk factors. PAR was estimated using average PAR. To apply PAR software, non-dichotomous independent variables needed dichotomization before estimation, which was conducted as follows: age <75 vs. ≥75, [3] NIHSS <4 vs. ≥4 (minor vs. moderate/major stroke), [3-5] On-admission SBP <140 vs. ≥140 mm Hg, [5] 24 Hr ARV-SBP and on-admission RBS by their median values (mentioned below). Analysis was carried out with R software, Version 3.5.1.

RESULTS

The analysis included 75 patients diagnosed with acute ischemic stroke who presented within 6 hours of onset. Their ages ranged from 35–90 and 28.6% were females. At the time of discharge, 29 (38.6%) patients had poor outcome. The 24-hr ARV index of both systolic and diastolic BP was calculated and divided into four quartiles as shown in Figures 1 and 2 along with their BI scores. The BI scores tend to decrease with each successive quartile of both 24-hr ARV-SBP (Q1-83 to Q4-53) and 24-hr ARV-DBP (Q1-76 to Q4-65). Simple univariate analysis was performed between the functional outcome and 24-hr ARV-SBP and 24 Hr ARV-DBP by grouping them into high and low ARV groups by median. The results are tabulated in Table 1. Twenty three (60.5%) of the patients with high 24-hr ARV-SBP were found to have poor functional outcome (P = 0.002 and 95% CI = 2.66–23.5) showing significant association between high ARV-SBP and poor outcome. However, the association between 24-hr ARV-DBP and poor outcome was not significant. Comparisons of baseline outcome predictors between the two groups of outcome and their unadjusted odds ratios and 95% CI by univariable logistic regression analysis are tabulated in Table 2. Categorization of age and NIHSS was based on a study conducted by Kim KI, et al., [25] and BMI was based on a study conducted by Yong M, et al. [16] In unadjusted logistic regression, age, sex, hypertension, on-admission SBP, on-admission RBS, 24-hr ARV-SBP, and NIHSS score were associated with poor outcome (P < 0.05). Upon multiple regression analysis, the outcome predictors found to be independent (p = <0.05) were as follows: age, NIHSS score, on-admission SBP, and 24-hr ARV-SBP [Table 3]. The PAR estimations of independent outcome predictors and their respective rankings are given in Table 3. 86.5% of the risk is attributable to the top five independent predictors, the highest being NIHSS score (26.4%) followed in order by 24-hr ARV-SBP (23.6%), age (18.5%), on-admission RBS (9.8%), and on-admission SBP (8.2%).

DISCUSSION

The findings of the present study place a greater importance on BPV as a target therapeutic risk factor and have important implications in the management of patients with acute ischemic stroke. 36.5% of the patients had poor outcome at discharge which is in accordance with prior
Table 1: Univariate analysis of patients with various high and low systolic and diastolic BP indices between good and poor outcomes groups

|                      | Poor Outcome (n=29) | Good Outcome (n=46) | Total (n=75) | p       | 95% CI       |
|----------------------|---------------------|---------------------|--------------|---------|--------------|
| 24-hr SBP            |                     |                     |              |         |              |
| ARV- Low (Q1 and Q2) ≤ 10.6 | 6 (16.2%)         | 31 (83.8%)          | 37 (100%)    | 0.002   | (2.66-23.5)  |
| High (Q3 and Q4)     | >10.6              | 23 (60.5%)          | 38 (100%)    | 0.09    | (0.16-1.11)  |
| Mean -Low (Q1 and Q2) ≤ 134 | 11 (28.9%)       | 27 (71.1%)          | 38 (100%)    | 0.004   | (1.33-19.6)  |
| High (Q3 and Q4)     | >134               | 18 (48.6%)          | 37 (100%)    | 0.112   |              |
| SD - Low (Q1 and Q2) ≤ 134 | 6 (15.7%)        | 32 (84.3%)          | 38 (100%)    | 0.004   | (1.33-19.6)  |
| High (Q3 and Q4)     | >134               | 23 (62.1%)          | 37 (100%)    | 0.112   |              |
| CV- Low (Q1 and Q2)  ≤11.2 | 7 (17.9%)         | 32 (82.1%)          | 39 (100%)    | 0.112   | (5.88-11.36) |
| High (Q3 and Q4)     | >11.2              | 14 (38.9%)          | 36 (100%)    | 0.112   |              |
| 24-hr DBP            |                     |                     |              |         |              |
| ARV - Low (Q1 and Q2) ≤ 7.47 | 16 (43.2%)        | 21 (56.8%)          | 37 (100%)    | 0.482   | (0.57-3.72)  |
| High (Q3 and Q4)     | >7.47              | 13 (34.2%)          | 25 (65.8%)   | 0.246   | (0.69-4.16)  |
| Mean -Low (Q1 and Q2) ≤ 77.6 | 18 (45%)          | 22 (55%)            | 40 (100%)    | 0.471   |              |
| High (Q3 and Q4)     | >77.6              | 11 (31.4%)          | 24 (68.6%)   | 0.471   |              |
| SD-Low (Q1 and Q2)  ≥ 9.57 | 15 (34.8%)        | 28 (65.2%)          | 43 (100%)    | 0.417   | (0.26-1.76)  |
| High (Q3 and Q4)     | >9.57              | 14 (43.7%)          | 18 (56.3%)   | 0.417   |              |
| CV-Low (Q1 and Q2)  ≤ 8.19 | 17 (36.1%)        | 30 (63.9%)          | 47 (100%)    | 1.297   | (0.71-6.71)  |
| High (Q3 and Q4)     | >8.19              | 12 (42.8%)          | 16 (57.2%)   | 1.297   |              |

The risk factors with p value <0.05 were written in bold and considered to be significant. ARV=Average real time variability, SBP, DBP=Systolic and diastolic blood pressure, Q=Quartile and CI=Confidence interval, SD=standard deviation and CV=coefficient of variation.
Thatikonda, et al.: BP variability as a target risk factor

NIHSS score (26.4%) which was found to have the highest PAR reported by majority of the studies. \cite{3-5} Though PAR of age (18.5%), on-admission RBS (9.8%), and on-admission SBP (8.2%) were found to be independent outcome predictors in the studies conducted by Carolin et al. \cite{3} and Davolin A, et al. \cite{21} they are ranked below BPV with ranks third, fourth, and fifth, respectively. \cite{3,21} This shows the relative importance of BPV compared to other predictors.

Given these findings, it is reasonable to hypothesize that reduction in BP variability during the acute phase of ischemic stroke might have a beneficial impact on the outcome of patients. However, there is a paucity of data directly comparing the predictive value of BPV, the timing and duration of BPV measurements, the practicality and acceptability of patients to the various BP measurement techniques, and how to best measure or define BPV. Further studies are needed on a large scale to determine the feasibility and efficacy of reducing BPV after stroke so that RCTs can be planned accordingly. The effects of antihypertensive agents on BP variability should be considered in ischemic stroke population and the classes of antihypertensives that exert

| Table 2: Outcome predictors at baseline and unadjusted associations with functional outcome of patients at the time of discharge assessed by univariable logistic regression analysis |
|---------------------------------------------------------------|
| **Outcome Predictors** | **Poor Outcome at Discharge** | **Univariable Logistic Regression** |
| | Yes | No | OR (95%CL) | p |
| Age (in yrs) Mean±SD | 62.2±11.9 | 58.4±14.2 | 1.05 (1.02-1.08) | <0.001 |
| Age Groups | | | | 0.09 |
| ≤65 | 3 (10.3%) | 9 (19.5%) | 1 |
| 66-75 | 16 (55.1%) | 23 (50%) | 2.26 (1.15-3.37) | 0.03 |
| 76-85 | 9 (31%) | 13 (28.2%) | 6.96 (3.2-10.66) | 0.02 |
| >85 | 1 (3.4%) | 1 (2.17%) | 1.76 (1.16-2.75) | 0.21 |
| Female Sex | 13 (44.8%) | 8 (17.3%) | 1.95 (1.11-3.48) | 0.03 |
| Stroke risk factors, Pre stroke | | | | 0.14 |
| BMI in kg/m² | 28.2±6.2 | 27.4±5.4 | 1.04 (0.98-1.09) | 0.12 |
| BMI Groups | | | | 0.14 |
| ≤25 | 8 (27.5%) | 16 (34.7%) | 1 |
| 25-29.9 | 11 (37.9%) | 19 (41.3%) | 0.89 (0.45-1.47) | 0.65 |
| ≥30 | 10 (34.4%) | 11 (23.9%) | 1.49 (0.36-1.17) | 0.44 |
| Hypertension | 18 (62%) | 28 (60.8%) | 3.06 (1.16-8.05) | 0.03 |
| Type 2 Diabetes mellitus | 11 (37.9%) | 19 (41.3%) | 0.86 (0.33-2.25) | 0.96 |
| Coronary artery disease | 5 (17.2%) | 10 (21.7%) | 0.75 (0.22-2.46) | 0.85 |
| Current smoking | 4 (13.7%) | 11 (23.9%) | 0.50 (0.14-1.78) | 0.44 |
| Regular alcohol consumption | 11 (37.9%) | 13 (28.2%) | 1.55 (0.57-4.16) | 0.53 |
| Atrial fibrillation | 11 (37.9%) | 12 (26.1%) | 1.73 (0.63-4.69) | 0.40 |
| Dyslipidemia | 5 (17.2%) | 7 (15.2%) | 1.16 (0.33-4.07) | 1 |
| Clinical Characteristics | | | | 0.08 |
| On-admission SBP Mean±SD | 159±27.2 | 140±23.4 | 7.18 (2.49-20.6) | <0.001 |
| On-admission RBS Mean±SD | 206±62.2 | 126±41.2 | 3.73 (1.36-10.1) | <0.001 |
| 24-hr ARV-SBP Mean±SD | 15.2±3.05 | 8.36±2.4 | 10.1 (3.11-22.2) | <0.001 |
| 24-hr ARV-DBP Mean±SD | 8.3±3.03 | 7.35±2.19 | 1.46 (0.57-3.72) | 0.57 |
| Etiologic subtype of ischemic stroke | | | | 0.08 |
| Large artery atherosclerosis | 7 (25%) | 13 (28%) | 1 |
| Cardiac embolism | 11 (36.5%) | 10 (20.8%) | 1.95 (1.11-3.48) | 0.03 |
| Small artery occlusion | 4 (13.5%) | 6 (15.1%) | 1.01 (0.49-2.03) | 0.96 |
| Stroke of another determined cause | 1 (2.9%) | 2 (4.34%) | 0.97 (0.24-3.03) | 0.85 |
| Stroke of undetermined cause | 6 (22.1%) | 15 (32.3%) | 0.77 (0.42-1.42) | 0.44 |
| NIHSS score, Mean±SD | 19.2±7.2 | 7.2±2.98 | 1.16 (1.08-1.23) | <0.001 |
| NIHSS Groups | | | | <0.001 |
| 0-4 | 1 (62.5%) | 6 (79.9%) | 1 |
| 5-15 | 11 (33.7%) | 13 (19.6%) | 2.20 (1.36-3.53) | 0.57 |
| ≥16 | 17 (3.8%) | 12 (1.17%) | 8.86 (1.92-51.71) | 0.08 |

The risk factors with p value <0.05 were written in bold and considered to be significant. SBP=systolic blood pressure, RBS=Random blood sugar, ARV=Average real time variability, NIHSS=National institute of health stroke scale, BMI=Body mass index, SD=Standard deviation, OR=Odds ration and CL=Confidence interval
target BP level and stability. Hence, large and multicenter studies are needed to evaluate the associations between BP variability and clinical outcome. To our knowledge, this is the first study to report the PAR value of the 24-hr BPV which is increasingly gaining attention in the field of stroke. It is also one of the few studies which have used ARV index to measure BPV which is more reliable. Although robust conclusions cannot be drawn because of limitations in the quality of the present study, it provides important novel information that the increased variability in BP in acute phase of ischemic stroke is related to poor functional outcome. This underlines the importance of BP monitoring in the early phase of ischemic stroke to warrant reasonable target BP level and stability. Hence, large and multicenter prospective studies have to be undertaken in future to elucidate the causality between BP and the clinical outcomes after acute ischemic stroke.

Clearly, there is further scope to explore BPV, how best to measure or define BPV, the timing and duration of BPV measurements, feasibility and efficacy of reducing BPV, and the practicality and acceptability of patients to the various BP measurement techniques. Such studies may be of help in guiding the clinical recommendations for BPV management.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Al-Hashel JY, Al-Sabah AA, Ahmed SF, Al-Enazi M, Al-Tawheidi N, Al-Mesailek Z. Risk factors, subtypes, and outcome of ischemic stroke in Kuwait: A national study. J Cerebrovascular Dis 2016;25:2145-52.
2. Bergström L, Irewall AL, Söderström L, Ögren J, Laurell K, Mooe T. One-year incidence, time trends, and predictors of recurrent ischemic stroke in Sweden from 1998 to 2010: An observational study. Stroke 2017;48:2046-51.
3. Malsch C, Liman T, Wiedmann S, Siegerink B, Georgakis MK, Tiedt S. Outcome after stroke attributable to baseline factors in the PROSCIS cohort with incident stroke (PROSCIS). PLoS One 2018;13:1-14.
4. Park TH, Ko Y, Lee SJ, Lee KB, Lee J, Han MK, et al. Identifying target risk factors using population attributable risks of ischemic stroke by age and sex. J Stroke 2015;17:302-11.
5. Grube MM, Koennecke HC, Walter G, Meisel A, Sobesky J, Nolte CH, et al. Influence of acute complications on outcome 3 months after ischemic stroke. PLoS One 2013;8:e75719.
6. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: A systematic review. Hypertension 2004;43:18-24.
7. Goldstein LB. Blood pressure management in patients with acute ischemic stroke. Hypertension 2004;43:137141.
Group. Blood pressure and clinical outcomes in the international stroke trial. Stroke 2002;33:1315-20.
9. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): A randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol 2009;8:48-56.
10. Bath PM, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, et al. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: A PROFESS subgroup analysis. Stroke 2009;40:3541-6.
11. 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;9:767-75.
12. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev 2014;10:CD000039.
13. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010;375:938-48.
14. de Havenon A, Bennett A, Stoddard GJ, Smith G, Chung L, O’Donnell S, et al. Determinants of the impact of blood pressure variability on neurological outcome after acute ischaemic stroke. Stroke Vasc Neurol 2017;2:e000057.
15. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, et al. Effects of 24-hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. Stroke 2011;42:3511-7.
16. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. Stroke 2008;39:366-72.
17. Al-Qudah ZA, Yacoub HA, Souayah N. Disorders of the autonomic nervous system after hemispheric cerebrovascular disorders: An update. J Vasc Interv Neurol 2015;8:43-52.
18. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 1991;29:231-40.
19. Tan Z, Meng H, Dong D, Zhao Y, Xu A. Blood pressure variability estimated by ARV is a predictor of poor short-term outcomes in a prospective cohort of minor ischemic stroke. PLoS One 2018;13:e0202317.
20. Chadachan VM, Ye MT, Tay JC, Subramaniam K, Setia S. Understanding short-term blood-pressure variability phenotypes: From concept to clinical practice. J Gen Intern Med 2018;11:241-54.
21. Davoli A, Motta C, Koch G, Dimedi M, Napolitano S, Giordano A, et al. Pretreatment predictors of malignant evolution in patients with ischemic stroke undergoing mechanical thrombectomy. J Neurointerv Surg 2018;10:340-4.
22. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: Clinimetric and clinical considerations. Clin Interv Aging 2013;8:201-11.
23. Rangaraju S, Haussen D, Nogueira RG, Nahab F, Frankel M. Comparison of 3-month stroke disability and quality of life across modified Rankin scale categories. Intervent Neurol 2017;6:36-41.
24. Tziomalos K, Giampatzis V, Bouziana SD, Spanou M, Kostaki S, Papadopoulou M, et al. No association observed between blood pressure variability during the acute phase of ischemic stroke and in-hospital outcomes. Am J Hypertens 2016;29:841-6.
25. Kim KI, Lee JH, Chang HJ, Cho YS, Youn TJ, Chung WY, et al. Association between blood pressure variability and inflammatory marker in hypertensive patients. Circ J 2008;72:293-8.
26. Tatasciore A, Zimarino M, Renda G, Zurro M, Socco M, Prontera C, et al. Awake blood pressure variability, inflammatory markers and target organ damage in newly diagnosed hypertension. Hypertension Res 2008;31:2137-46.