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Blood Pressure Variability and Shifting in Clinical Outcome Amongst Stroke Patients in Southwestern Uganda.

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Background: Higher blood pressure variability is associated with shifting towards worse outcome among stroke patients. **Methods:** We conducted a prospective cohort study of CT head confirmed ischemic and hemorrhagic stroke admitted within 7 days of onset of motor weakness. Blood Pressure Variability (BPV) indice; Standard Deviation (SD) of systolic and diastolic Blood pressure (BP) between 0 and 7 days after admission was calculated with subsequent modified Rankin Scale (mRS) score on day 14 and day 30 post-stroke. Ordinal logistic regression was fitted to determine the adjusted odds ratios (aOR) for shifting towards worse clinical outcome at 30 days among patients with stroke that had survived beyond 14 days with 95% CI and p value<0.05 used as statistical significance. **Results:** Out of 120 patients, 32 patients passed on by day 14, 88 patients survived beyond day 14. Fourteen patients had a 1 point shift in MRS towards worse outcome at 30 days of stroke onset. Blood pressure variability SD systolic BP tertiles (2&3) had aOR: 1.6, p= 0.306 (95%C.I: 0.6-4.1) and 5.8, p = 0.002 (95%C.I: 1.9-17.5) respectively. NIHSS≥16 had aOR=3.8 (95%CI: 1.5-9.6) P=0.004 and time to presentation ≥ 3 days had aOR=2.8 (95% C.I:1.2-6.3) p=0.013. **Conclusion:** Higher BPV (tertile 3), late presentation ≥ 3 days and high NIHSS conferred statistically significant odds of shifting towards a bad functional outcome.

Key words: Blood pressure variability; Stroke; outcomes; cerebral infarction; intracerebral hemorrhage; Sub-Saharan Africa

Introduction

Blood pressure variability refers to continuous fluctuations in blood pressure and it has been noted to be increased in patients with acute stroke (1, 2). There is a rise in stroke occurrence in low- and middle-income countries (LMICs) with Africa having a high fatality rate (3). In Uganda, studies have shown a high 30-day mortality at 26.8% - 38.1% (4-6). A growing population with high burden of uncontrolled hypertension has

resulted in high rates of strokes, which is a key modifiable risk factor (7, 8). Blood pressure (BP) changes occur immediately after a stroke to restore impaired cerebral autoregulation (9, 10). Autoregulation plays a vital role in the regulation of brain blood flow and perfusion however it has been shown to fail after acute stroke (11). The brain is sensitive to blood pressure changes hence lower perfusion impairs tissue oxygenation, while excessive perfusion results in the breakdown of the blood brain barrier causing injury to the brain (12).

The uncontrolled elevation of BP in patients with hemorrhagic stroke via the Cushing reflex and major stroke related stress (12, 13) can lead to hematoma expansion which may result in neurological deterioration, while in ischemic stroke can potentially increase the risk of hemorrhagic transformation (14). Hence higher blood pressure variability has cumulative detrimental effects on clinical outcome of patients with both types of stroke (15). Earlier studies have showed that high blood pressure variability is associated with shifting towards worse outcomes among those who have survived a stroke (16). And some have related high blood pressure variability with increased mortality (17). Independent of BP level, higher BP variability (BPV) after ischemic and hemorrhagic stroke is also associated with poor functional outcome and death (18).

Blood Pressure Variability is divided into very short term variability (beat to beat), short term variability (24 hour BPV), medium term variability (day to day BPV), long term variability (visit to visit BPV less than 5 years) and very long term variability less than or equal 5 years) (1). Variation in BP is the sum of responses to extrinsic pressor stimuli, and intrinsic pressor stimuli (19) (1) (20). It is measured using standard deviations (SD), coefficient of variation (CV), Average real variability (ARV), variability independent of mean (VIM) and residual blood pressure variability (RBPV) (21). Ambulatory BP monitoring (ABPM) provided evidence that an initial increase in BPV is an independent predictor of cardiovascular complications like stroke (22).

The association of BPV with shifting in worse neurological outcomes after stroke warrants further investigation. The magnitude to which systolic BP lowering influences outcome has been linked heavily on the size of the hematoma (23). Severe stroke has been associated with greater disturbance in the autonomic nervous system resulting in higher BP fluctuations hence the bidirectional causality between BPV and outcome cannot be excluded (23). In Sub-Saharan Africa, there are few studies that have evaluated the effect of blood pressure variability on shifting in clinical outcome among 14 days survivors after a stroke. Hence we designed a cohort to determine blood pressure variability and shifting in clinical outcome amongst patients with stroke presenting to a tertiary hospital in Southwestern (SW) Uganda.

METHODS

Study design and participants

This study was a prospective cohort of patients with acute and subacute stroke admitted to Mbarara Regional Referral Hospital, a tertiary hospital in SW Uganda. We included patients 18 years of age and older with sudden onset of focal neurological deficits within 7 days, and non-contrast

Computerized Tomography (CT) head proof of ischemic or hemorrhagic stroke. We excluded patients with traumatic intracerebral hemorrhage such as subdural hematomas, epidural hematomas, and traumatic brain injury and those who died or were lost to follow up before completion of one day of blood pressure measurement. On admission, all patients were positioned with the head of the bed elevated at 30 degrees to prevent aspiration, and oxygen saturation was kept above 93% as the standard of care. An initial blood pressure was measured using EDAN M3® (Edan USA 2014). Three blood pressure values were taken on admission and the average of the last two was considered the blood pressure at hospital admission. (24). Socio-demographics (like age, sex, marital status) and lifestyle factors (like smoking and alcohol history) were captured. Past medical records were evaluated to capture history and duration of hypertension, diabetes mellitus, types of medications prescribed, presence of co-morbid kidney disease and heart disease. A complete clinical examination was conducted which included the Mayo Clinic Full Outline of Unresponsiveness (FOUR) score to evaluate the level of consciousness and the National Institutes of Health Stroke Scale (NIHSS) score to assess stroke severity. Stratification of the NIHSS score was as follows: 1-4 = minor stroke, 5-15 = moderate stroke, 16 to 20 = moderate to severe stroke, and 21 – 42 = severe stroke (25).

Laboratory procedures

Capillary blood glucose was measured using Accuchek glucometer (Roche Diagnostics Inc.). Total Cholesterol (TC) was measured using an enzymatic linked immunosorbent assay method in a Human 200 analyzer (German Design, Human Diagnostics), renal function tests, serum Sodium and potassium were measured using Sysmex XNL-550®.

Blood pressure monitoring

After the initial clinical evaluation, admission blood pressure was measured, then follow-up blood pressures were measured at intervals of 6 hours (6 am, noon, 6 pm and midnight) using a standard noninvasive automated BP monitoring device EDAN M3® (EdanUSA 2014) on the non-paralytic arm up to day 7 post-stroke. The measurement interval was adopted from the European Cooperative Acute Stroke Trial (ECASS) which investigated the characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke (26). Each time the blood pressure was measured, 2 readings were taken, and both mean systolic and diastolic blood pressure were calculated and subsequently recorded as the blood pressure of the patient.

Outcome Measures

The primary outcome was shifting towards worse outcome at 30 days among patients that had survived beyond 14 days of stroke onset. Additionally, a modified Rankin Scale (mRS) score, which is a measure of the degree of neurological disability was assessed as the outcome at day 14 and day 30 post-stroke (27).

Ethical considerations:

The study was approved by the Institutional Review Board (IRB) at Mbarara University of Science and Technology (ID: MUST-2021-118) and Uganda National Council of Science and Technology (ID: HS1973ES). Participants that had capacity to consent provided written informed consent and in those that did not have capacity, consent was obtained from a surrogate decision maker.

Statistical Analysis

Clinical characteristics were computed as mean, and standard deviation for normally distributed variables. Categorical variables were summarized in frequencies and percentages. We used a student's t-test for continuous variables and chi-square test to demonstrate a difference in the baseline characteristics between patients with hemorrhagic stroke and ischemic stroke.

Blood pressure variability was expressed as Standard Deviations (SD) (SDSBP), and Coefficient of variation (CV) (CVSBP) of Systolic and Diastolic BP respectively.

SD = $\sqrt{\sum (SBP - SBP_{mean})^2 / n}$, and CV = $[(SDSBP / BP_{mean})] 100]$. To standardize the analyses, BPV indice were categorized into tertiles so that each contained a third of the cohort (i.e. tertile 1, tertile 2 and tertile 3). The use of tertiles allowed for the existence of linearity. Ordinal logistic regression analysis was fitted to determine the factors associated with shifting towards worse outcome among patients that had survived beyond 14 days of stroke onset at 5% level of significance to determine the odds ratios, 95% confidence interval and p - value.

RESULTS

We screened 276 eligible patients with unilateral neurological deficits between August 2021 and April 2022. We enrolled 120 patients with confirmed strokes on CT head (figure 1); 52.5% had ischemic stroke and 47.5% had hemorrhagic stroke (Table 1). Out of 120 patients, 32 patients passed on by day 14 and 88 patients with stroke survived beyond 14 days of stroke onset. The overall median age was 65 years (IQR: 54-80). History of smoking and excessive use of alcohol was elicited in 21.6% and 40% of all patients respectively. Patients with ischemic stroke were older, with a high diagnosis of diabetes mellitus and a high blood sugar at admission, while patients with hemorrhagic stroke had higher NIHSS scores, mean systolic blood pressure and mean diastolic blood pressure at admission (Table 1). Patients with hemorrhagic stroke had a higher mean SBP compared to ischemic stroke with the first 7 days of stroke onset (Figure2). There was a statistical difference between hemorrhagic and ischemic stroke with mean DBP (92 mmHg vs 85 mmHg) with p = 0.04 respectively.

p=0.017 respectively (table 2)

Primary outcome

Patients that survived beyond 14 days post stroke, 14 patients shifted towards bad outcome at 30 days. Using ordinal logistic regression to evaluate the factors associated with shifting towards worse outcome, we found that late presentation of more than 3 days, severe stroke (NIHSS≥16) and Blood pressure variability tertile 3 conferred statistically significant odds ratios; aOR= 2.9, p-value=0.009, aOR=3.5, p-value=0.016, and aOR=4.3,

DISCUSSION

In this study our objective was to determine the effect of blood pressure variability (BPV) measured using standard deviation (SD) on shifting towards worse outcome at 30 days of stroke onset among patients that had survived a stroke beyond 14 days. We found that high SDBP conferred statistically significant odds of shifting towards worse outcome. We also found that patients with severe stroke and those who presented to the hospital late conferred statistically significant odds of shifting towards worse outcome. These findings relate with earlier studies of worsening clinical outcome after a stroke with rising SDBP. Blood pressure variability using SD has been assessed in many post-stroke studies and is good estimate of BPV (23).

Over all, patients with hemorrhagic stroke that had survived beyond 14 days had higher overall BPV in both systolic and diastolic blood pressure compared to ischemic stroke. However, our BPV values are much lower compared to those of Fischer et al where a SDSBP of 37.6 mmHg in hemorrhagic stroke and a 30.5 mmHg in ischemic stroke was measured in the first 24 hours of stroke onset. Using different methods of Blood Pressure assessment likely contribute to disparate results. For example, the use of an automated BP monitor in our study at fixed intervals versus ambulatory BP monitoring and invasive BP monitoring in other studies, and the fact that BP measurements were taken within 24 hours of stroke in the previous studies compared with up to 7 days in our study, may explain some of the differences. The automated BP monitor likely underestimates the mean arterial pressure (MAP) and Diastolic Blood Pressure compared with intra-arterial measurements, but SBP values may be similar (28).

We also found that, high BPV, severe stroke defined using NIHSS ≥16 and late presentation to hospital of more than 3 days confirred statistically significant odds of shifting towards worse outcome among stroke patients. In hemorrhagic stroke, high blood variability increases hematoma expansion thus worsening the clinical outcome of patients (29) while in ischemic stroke, the penumbra is particularly sensitive to negative effects of cerebral perfusion fluctuations caused by high blood pressure variability (30). Rapid falls in blood pressure increase the peril of tissue ischemia expansion and reduce the chance of reperfusion, while a rapid increase in blood pressure increases the risk of hemorrhagic transformation (31).

Patients with severe stroke may translate to lager volume core affected with a larger degree of vascular disruption which leads to an increase in the rate cerebral autoregulation leading to high levels of blood pressure fluctuations, increase brain edema, and intracranial pressure, and also brain cell mass death leading to high risk of hemorrhagic transformation in ischemic stroke and hematoma expansion in hemorrhagic stroke (32, 33). Stroke related infections are common in patients with severe stroke and have been reported in upto 64% developing in 3 days of stroke onset hence contributing to shifting towards worse outcome (34).

Patients who presented late to the hospital had high odds of shifting towards worse outcome as there is delayed intervention to halt the stroke expansion, brain cell death and stroke related infections hence contributing to worse outcome among stroke patients (5). Delayed arrival might have been attributed to failure to recognize stroke signs and symptoms, lack of transportation, distance

from the hospital, lack of awareness about the importance of early arrival to the hospital for treatment of stroke (35).

This study adds to the growing literature on the factors associated with shifting towards worse outcome among stroke patients (36-38). These findings are particularly key when considering options for BP reduction after stroke and which medications are more efficacious in reducing BPV. They are also particular in considering early presentation to hospital. Larger-scale trials are needed to confirm our findings and explore the mortality and disability implications of successful and widespread interventions aimed at reducing BPV, and early presentation to hospital.

Limitations of the study, This study was limited to only patients that were admitted in a tertiary hospital which is known for having very sick patients. Patients with small strokes were less likely represented in our study since there had to be CT head confirmation of stroke before inclusion.

In conclusion, we have provided evidence that high BPV, late presentation and severe stroke are associated with shifting towards worse outcome in SW Uganda.

List of abbreviations

BP: Blood Pressure, BPV: Blood Pressure Variability, CT: Computed tomography, CVA: Cerebrovascular accident, MRRH: Mbarara Regional Referral Hospital, mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, SD: Standard Deviation, SDDBPV: Standard Deviation Diastolic Blood Pressure Variability, SDSBPV: Standard Deviation Systolic Blood Pressure Variability

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The authors named in this manuscript contributed substantially to this research work and met the criteria for authorship. Nicholas Kulaba, Adrian Kayanja, and Anthony Muyingo took part in the conception of the research idea, development of the research project, elaboration of the research protocols, and correction of the manuscript and approved the final manuscript. Mark Kaddu Mukasa, Martin Kaddumukasa, Jane Nakibuuka, and Shirley M. Moore took part in the correction of the research project and protocols, manuscript writing, and approval of the final manuscript. Denis Serubiri and Sophia Najjingo took part in data collection, data interpretation, manuscript revision, and approval of the final manuscript.

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