Treatment of Hypertension in Acute Ischemic Stroke

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Introduction:
There has been substantial controversy regarding treatment of blood pressure in the management of acute ischemic stroke.

Aim of the study:
To study stroke outcome in relation to treatment of hypertension in the management of acute ischemic stroke and its impact on the cardiovascular system.

Patients and methods:
This was a prospective study in which all admitted patients for acute ischemic stroke within 24 hours throughout the year 2006 were included. The severity of the stroke was based on the National Institutes of Health Stroke Scale (NIHSS). The 2005 AHA/ASA guidelines in the management of acute ischemic stroke were followed. We also followed the same guidelines in the treatment of hypertension in adults with acute ischemic stroke in the first 24 hours. However, patients who continued to have hypertension grade II&III after the first 24 hours were also treated.

Results:
A total of 241 completed the study and attended the clinics for their follow up assessment at 3 months. The majority were males (76%), preexisting hypertension was found in 68.9% and most of the patients had hypertension on admission (87.5%). In 223 patients (92.53%) no antihypertensive medication was given in the 1st 24 hours. In 134 patients (55.6%) the blood pressure continued to be on the hypertensive side after the first 24 hours and they received antihypertensive medications. The 223 patients (92.53%) who did not receive antihypertensive treatment achieved 57.1%, 78.09% and 73.87% of the total reduction in SBP, DBP and MBP respectively at the end of the 1st 24 hours. All cardiac complications (ten patients, 4.15%) were reported in the first 24 hours only. The mean NIHSS score on admission was 22.98±10.38, while the mean score at the 3rd month was 9.4±6.5. The differences were highly significant (p< 0.0001). When the stepwise regression analysis was used, only the increase in stroke severity at the onset (p<0.0001), followed by the decrease in SBP at the 3rd day (p< 0.001) and lastly the increase in SBP on admission (p< 0.05) were predictive for poor stroke outcome.

Conclusion:
Introducing antihypertensive medications after the first 24 hours of acute ischemic stroke in patients who continued to have hypertension grade II&III has no negative impact on stroke outcome and limits the cardiovascular complications.
**Introduction:**

In the year 2000, there were approximately 20 million strokes worldwide, making cerebrovascular disease the sixth leading cause of disability, a burden predicted to rise substantially by 2020. Approximately one quarter of all strokes are fatal, and at least one third nonfatal strokes result in long-term disability or dependency. (1-5)

Hypertension is the most prevalent modifiable risk factor for ischemic stroke. Approximately two-thirds of the cerebrovascular disease burden is attributable to nonoptimum blood pressure. Blood pressure (BP) levels are positively and continuously associated with the risk of stroke in a long-linear fashion for the first-ever and recurrent stroke. (6,7) Lowering BP reduces the risk, both in primary and secondary prevention, and larger reduction in BP produce larger reductions in stroke risk. (8).

However, unlike the well-established knowledge of BP management to prevent stroke, few data are available about handling BP in the acute setting. The pathophysiology of high BP in acute stroke is complex and poorly understood, and there is a lack of adequate evidence to guide therapeutic decisions. (9) Data to guide recommendations for treatment are inconclusive or conflicting. More studies are still needed to guide the treatment of hypertension in acute stroke settings. (10,11)

There are concerns that persistent high level of blood pressure may lead to myocardial dysfunction considering the high rate of concomitant cardiac disease in patients with acute cerebrovascular events. Also stroke patients are known to have increased sympathetic activities and high level of plasma catecholamines which may produce cardiac dysfunction.(12-14)

**Aim of the work:**

To study stroke outcome in relation to treatment of hypertension in the management of acute ischemic stroke and its impact on the cardiovascular system.

**Patients and methods:**

This was a prospective study that was carried out on all adult patients who were admitted with acute ischemic stroke to Hai Al-Jamea Hospital, Jeddah, K.S.A. throughout the year 2006. The study was approved by the hospital ethics committee.

Upon emergency room (ER) admission, blood samples were taken, and a cranial computed tomography (CT) was immediately performed to rule out hemorrhage or other non ischemic causes of the ictus. Then patients were transferred to the stroke center. A thorough history and full neurological assessment with recording of neurological deficits and state of consciousness was performed. Only patients with acute ischemic stroke within 24 hours were included. Onset time was defined as the last time the patient was known to be in his/her usual state of health. The admitting neurologist provided the severity of the stroke based on the National Institutes of Health Stroke Scale (NIHSS),(15) The stroke severity was categorized as mild (NIHSS score 0-5), moderate (NIHSS score 6-15), severe (NIHSS score 16-25), and very severe (NIHSS score >25)
Blood pressure (BP) was measured by the traditional Riva Rocci method using an arm cuff and a sphygmomanometer. Systolic BP (SBP) and diastolic BP (DBP) values were noted and mean BP (MBP) values were calculated according to the formula MBP=DBP+1/3 (SBP–DBP). History of hypertension and whether or not they were taking antihypertensive agents were also reported from the patients, their families or from their hospital charts. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. For statistical analysis, SBP, DBP and MBP were reported at admission, 12 hours, 24 hours, end of the 2nd and 3rd day. Hypertension was graded into 3 grades: grade 1, grade 2, grade 3. (Table 1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

Cardiac troponin I was done to all patients. Also, ECG was done to all patients looking for ST segment shift and QT interval. Echo Doppler was done for patients with heart failure or ECG changes.

Management of patients was generally done according to the American Heart Association/American Stroke Association (AHA/ASA) 2003 guidelines for the early management of patients with ischemic stroke (10) and its update in 2005 (18). In the treatment of hypertension, we followed the same guidelines in the first 24 hours; i.e., only those who had SBP>220 and /or DBP>120, received antihypertensive treatment in the first 24 hours and also those who had blood pressure below that limit but had end-organ involvement (e.g., aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy) received treatment. However, patients who continued to have grade II & III hypertension after the first 24 hours received treatment. Antihypertensives were chosen at the discretion of the treating physician (16).

After discharge, patients were followed in the out patients clinic and the severity of the stroke was reassessed at the 3rd month based on the NIHSS.

Statistics:

Statistical analysis was performed with the SPSS software package. Continuous data were presented as mean/SD and categorical variables as numbers/percentage. Student unpaired t tests were used for comparison of patients groups and for testing of continuous variables. Two multiple linear regression models were tested. In the first model we tested the risk factors (independent variables) that would predict the stroke severity at onset (NIHSS scores on admission) (the dependent variable). Age, gender, history of arterial hypertension, diabetes, smoking status, dyslipedemia, coronary heart diseases, SBP, DBP and MBP on admission were the risk factors (independent variables) studied in this model. In the 2nd model, we tested the risk factors (independent variables) that would predict stroke outcome (NIHSS scores on the 3rd month) (the dependent variable). Beside the above risk factors that were used in the first model, stroke severity at the onset (NIHSS scores on admission) and the
successive MBP, SBP and DBP measures to the end of the 3rd day were also used as independent variables in this model. In both models we first used “enter” method to test the weight of all the risk factors on the prediction of the dependent variable. If the model was statistically significant then we used the “stepwise” method to find the risk factors that are statistically of high significance in the prediction of the dependent variable.

**Results:**

A total of 356 patients were initially included and managed in the acute phase. Only 241 completed the study and attended the clinics for their follow up assessment at the 3rd month. Table 2 shows the basic characteristics of the patients. To be noted that: the majority was males (76%), preexisting hypertension was of high incidence (68.9%) and most of the patients had hypertension on admission (87.5%). Seventy two patients (29.86%) had grade I hypertension, 48 patients (19.9%) had grade II hypertension, and 90 patients (37.34%) had grade III hypertension. The mean SBP was 159±26.37 mmHg, the mean DBP was 94.63±15.48 mmHg, while the mean MBP was 116.1±17.18 mmHg.

Only 18 patients (7.47%) received intravenous antihypertensive medications in the 1st 24 hours (SBP > 220mmHg and/or DBP >120mmHg). In the remaining 223 patients (92.53%) no antihypertensive medication was given in the 1st 24 hours. In 134 patients (55.6%) the blood pressure continued to be on the hypertensive side after the first 24 hours and they received antihypertensive medications.

The total reduction in blood pressure over the study period (3 days) was calculated for SBP, DBP and MBP by subtracting the final readings at the end of the third day from the initial readings on admission. The reduction over each period was calculated similarly (table 3) and the percentage relative to the total reduction was calculated. Excluding patients who received I.V. antihypertensive medications in the 1st 24 hours (18 patients), the other 223 patients (92.53%) achieved 38.36% and 57.1% of the total reduction in the SBP by the first 12 and 24 hours respectively, 73.57% and 78.09% of the total reduction in the DBP by the first 12 and 24 hours respectively, 55.48% and 73.87% of the total reduction in the MBP by the first 12 and 24 hours respectively.

All cardiac complications (ten patients, 4.15%) were reported in the first 24 hours only. The ten patients had hypertension. Three patients (1.24%) developed acute pulmonary edema, of whom one had blood pressure of 240/120 mmHg with no history of cardiac disease, the second presented with blood pressure 200/95 with no history of cardiac disease & the third had blood pressure of 180/90 with history of ischemic cardiomyopathy. All those patients received intravenous medications to manage pulmonary edema. ECG, transthoracic echocardiography and serum troponine were assessed in those three patients.

Four patients (1.66%) presented initially with grade III hypertension (but SBP < 220 and/or DBP <120) and developed non ST segment elevation myocardial infarction (non STEMI). Their ECG showed ST-T wave changes with elevated serum troponin. Three of them (1.24%) had typical chest pain, while the fourth had silent infarction. Transthoracic echocardiography was done for these patients to assess segmental wall
motion abnormalities and left ventricular function. Their blood pressure was controlled by four antihypertensive medications.

Three patients (1.24%) had previous history of ischemic heart disease - documented by coronary angiography or non invasive tests – and showed new ST-T wave changes without elevation of the serum troponine. Two of them did not have chest pain while the third had typical chest pain. Two of them presented with grade III hypertension (but SBP < 220 and/or DBP <120) and the third with grade II hypertension.

Four patients (1.66%) developed transient ST segment depression of > 1mm on serial ECG tracings with negative enzymes and absent cardiac symptoms. Doputamine echocardiography was done later on and was negative for ischemia.

Table 2: Baseline factors for the 241 patients studied.

<table>
<thead>
<tr>
<th>Baseline factors</th>
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<tbody>
<tr>
<td>Age, (mean ± SD), y</td>
<td>56.75±13.49</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>76</td>
</tr>
<tr>
<td>Nationality; Saudi, %</td>
<td>51</td>
</tr>
<tr>
<td>Blood pressure on admission:</td>
<td></td>
</tr>
<tr>
<td>SBP, (mean ± SD), mmHg</td>
<td>159±26.37</td>
</tr>
<tr>
<td>DBP, (mean ± SD), mmHg</td>
<td>94.63±15.48</td>
</tr>
<tr>
<td>MBP, (mean ± SD), mmHg</td>
<td>116.1±17.18</td>
</tr>
<tr>
<td>Hypertension on admission, %</td>
<td>87.5</td>
</tr>
<tr>
<td>Preexisting hypertension, %</td>
<td>68.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>51.3</td>
</tr>
<tr>
<td>Dyslipidemic, %</td>
<td>57.5</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>4.7</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>36.8</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>3.6</td>
</tr>
<tr>
<td>Smoking habits, %</td>
<td>42.9</td>
</tr>
<tr>
<td>Baseline NIHSS, (mean ± SD)</td>
<td>22.98±10.38</td>
</tr>
<tr>
<td>NIHSS at 3 months, (mean ± SD)</td>
<td>9.4±6.5</td>
</tr>
</tbody>
</table>

Table 3: The reduction in blood pressure throughout the three days.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Changes over the 1st 12 hours (mean±SD)</th>
<th>Changes over the 2nd 12 hours (mean±SD)</th>
<th>Changes over the 1st day (mean±SD)</th>
<th>Changes over the 2nd day (mean±SD)</th>
<th>Changes over the 3rd day (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>19.61±7.27</td>
<td>7.00±3.36</td>
<td>20.26±5.9</td>
<td>4.90±3.92</td>
<td>3.80±2.12</td>
</tr>
<tr>
<td>DBP</td>
<td>5.30±2.80</td>
<td>2.10±1.20</td>
<td>6.12±2.6</td>
<td>1.63±0.46</td>
<td>1.20±0.11</td>
</tr>
<tr>
<td>MBP</td>
<td>8.80±2.25</td>
<td>3.73±0.88</td>
<td>9.76±3.8</td>
<td>2.72±1.86</td>
<td>2.65±1.34</td>
</tr>
</tbody>
</table>
The mean NIHSS score on admission was 22.98±10.38, while the mean score at the 3rd month was 9.4±6.5. The differences were highly significant (t = 15.59, p< 0.0001). (Figure 1) Fifty one patients showed improvement on the NIHSS by less than 10 points, 81 patients (33.61%) showed improvement by 10 to 20 points, and 109 patients (45.23%) showed improvement by more than 20 points. (Table 4)

To test for the factors that would predict the stroke severity at onset, multiple linear regression analysis was carried out. In this model, stroke severity at onset (measured by the NIHSS scores on admission) was used as the dependent variable while the age, gender, history of arterial hypertension, diabetes, smoking status, dyslipidemia, coronary heart diseases, SBP, DBP and MBP on admission were used as the independent predictors. When the enter method was used, the model was found statistically significant (R Square = 0.34, F = 2.936, p< 0.05). None of the risk variables were excluded from the analysis. When the stepwise regression method was used (R Square= 0.305, p< 0.0001), only increasing age (B = 0.338, p<0.001), male sex (B = 7.654, p< 0.01) and history of hypertension (B = 3.547, P< 0.01) were found highly predictive of higher stroke severity at onset (constant = 11.8).

To test for the factors that would predict the stroke outcome (measured by the NIHSS scores at the 3rd month), multiple linear regression analysis was carried out. In this model the dependent variable was the NIHSS scores on the 3rd month and the independent predictors were the same risk factors used in the previous regression model (age, gender, history of arterial hypertension, diabetes, smoking status, dyslipidemia, and coronary heart diseases), in addition to the stroke severity at onset (measured by the NIHSS scores on admission), the successive SBP, DBP and MBP readings over the 3 days of the study and the changes in the MBP between the first day, end of second and third days. When the enter method was used in the analysis, the model was found highly statistically significant (R Square = 0.87, F = 8.96, p < 0.0001). The variables finally included statistically were the SBP readings and the differences in the MBP between the first day and end of second and third days. The variables excluded were all the MBP measures, and the DBP measures. When the stepwise regression method was used (R Square = 0.814, p<0.0001), only the increase in stroke severity at the onset (B = 0.562, p<0.0001), followed by the decrease in SBP on the 3rd day (B = −0.084, p< 0.001) and lastly the increase in SBP on admission (B = 0.046, p< 0.05) were predictive of poor stroke outcome (constant = 1.246). The other variables were excluded from the model.

Table 4: Showing the improvement of patients at the 3rd month on the NIHSS

<table>
<thead>
<tr>
<th>Improvement on the NIHSS</th>
<th>n (%)</th>
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<tr>
<td>&lt;10 points</td>
<td>51 (21.16%)</td>
</tr>
<tr>
<td>10-20 points</td>
<td>81 (33.61%)</td>
</tr>
<tr>
<td>&gt; 20 points</td>
<td>109 (45.23%)</td>
</tr>
<tr>
<td>Total</td>
<td>241 (100%)</td>
</tr>
</tbody>
</table>
Figure 1: Stroke severity on admission and after 3 months as assessed by the NIHSS
Discussion:

Hypertension is extremely common in acute stroke patients. Several recent studies have documented that blood pressure is frequently elevated in the first day or so of stroke (18,19,20). In the present study, 87.5% of the patients had hypertension on admission; seventy two patients (29.86%) had grade I hypertension, 48 patients (19.9%) had grade II hypertension, and 90 patients (37.34%) had grade III hypertension. Blood pressure elevations in acute stroke may be mediated by a variety of mechanisms, including pre-existing hypertension, but also stress associated with the acute illness and hospitalization, increased sympathetic drive with catecholamine and cortizol release, activation of the rennin-angiotensin-aldosterone system, and the Cushing reflex in cases of markedly increased intracranial pressure due to intracerebral hematoma or edema (21,22). In addition, transient elevation in blood pressure may in some cases be compensatory: Lindsberg (23) and Mattle and co-workers (9) reported that blood pressure elevations are seen with vascular occlusion and normalize following recanalization of the occluded vessel.

Although it is widely agreed that treatment of high blood pressure is essential for stroke prevention, there has been substantial controversy regarding treatment of blood pressure in the management of acute ischemic stroke. Theoretical reasons to lower the blood pressure include reducing the formation of brain edema, lessening the risk of hemorrhagic transformation of the infarction, preventing further vascular damage, and forestalling early recurrent stroke. However, aggressive treatment of elevated blood pressure could be detrimental because of secondary reduction of perfusion in the area of ischemia, which could expand the size of the infarction. On the other hand, blood pressure declines spontaneously over the first 3 to 10 days after acute ischemic stroke and returns to pre-stroke levels in two thirds of patients; 40% of patients remain hypertensive. (17,24) This spontaneous reduction in blood pressure was also seen in the present study. The 223 patients (92.53%) who did not receive antihypertensive medications in the first 24 hours achieved 38.36% and 57.1% of the total reduction in the SBP, 73.57% and 78.09% of the total reduction in the DBP and 55.48% and 73.87% of the total reduction in the MBP by the first 12 and 24 hours respectively.

In reviewing the literature, studies that investigated the relationship of acute blood pressure to outcome have revealed conflicting findings. Some investigators have documented better outcome in association with higher acute blood pressure (25,26), while others have demonstrated improved functional recovery and lower incidence of edema associated with a 20-30% drop in mean arterial pressure (MAP) (27), even when blood pressure reduction was not the result of active treatment (28). Still other studies reported a complex pattern, with poor outcomes at extremes of the spectrum (29-32).

The decision of when to treat hypertension has been further complicated by the interaction between the central nervous system and the cardiovascular system during acute cerebrovascular events.(33,34) Although ST segment and T-wave changes in the ECG are well-known consequences of stroke,(35) arrhythmias (36) and cardiac autonomic changes (37) have also been reported. All these abnormalities seem to be associated with lesions of autonomic cardiac control centers. (33,37,38) On the other hand, hypertension has long been considered the most potent risk factor for cardiovascular diseases (39,6). The Framingham Heart Study in the United States
found that hypertension is a significant risk factor for both cerebrovascular and ischemic heart diseases (40).

Unfortunately, despite the presence of this uncertainty and in the absence of clear guidelines, the treating physician has to make a decision in number of issues that have not gain consensus yet. In the present study we chose to follow the 2005 guidelines in the treatment of hypertension in adults with acute ischemic stroke in the first 24 hours; i.e., not only those who had SBP>220 and /or DBP>120, received antihypertensive treatment in the first 24 hours but also those who had blood pressure below that limit but had end-organ involvement (e.g., aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy) received treatment. However, we also chose to treat patients who continued to have moderate to severe hypertension after the first 24 hours. In this way, the high blood pressure was left to drop spontaneously over the most critical period of acute ischemic stroke, but without compromising the other end organs, most importantly the cardiovascular system.

Leaving the blood pressure to drop spontaneously in the first 24 hours in most of the patients and treating those patients who continued to have hypertension after that resulted in a very good stroke outcome. The mean NIHSS score on admission was 22.98±10.38, while the mean score at the 3rd month was 9.4±6.5. The differences were highly significant (t = 15.59, p< 0.0001). Fifty one patients showed improvement on the NIHSS by less then 10 points, 81 patients (33.61%) showed improvement by 10 to 20 points, and 109 patients (45.23%) showed improvement by more than 20 points. On the other hand, starting antihypertensive medications after the first 24 hours limited cardiac complications which occurred in the first 24 hours.

The result of the stepwise regression analysis showing that the decrease in SBP at the 3rd day was predictive of poor stroke outcome need to be interpreted cautiously in view of many other findings. First, almost 60% of the total reduction in the SBP had been already achieved spontaneously by the end of first 24 hours. Secondly, the continued spontaneous decline in BP after the first 24 hours was reported by previous stroke trials (17,24). Thirdly, antihypertensive medications were used in 50% of patients only and most of these drugs have a slow mode of action. Lastly, theoretical considerations and observational evidences suggest that the blood pressure lowering agents may affect the outcome, independent of blood pressure lowering (41,42). In support to that, the stroke outcome in this study was very good. So, the result of the stepwise regression is not against the use of antihypertensive medications after the 1st 24 hours.

There is little evidence to date regarding the effects of individual classes of blood pressure-lowering agents in acute stroke, but It was not the intention of the current authors to study a particular antihypertensive medication or to compare between their different classes. So, it was left to the discretion of the treating physician to choose the best to every patient according to his medical profile. The variability among the different classes used had lessened the statistical power of any class or particular medication and the drug effect was excluded from the stepwise regression analysis.

Since we have believed, to the best of our knowledge and experience, that the current management protocol has been providing the best chance to our patients, it was
unethical to design a double blind control study in which the control patients would have been provided a different management that carried at least a theoretical risk of harm. This management would have breached the venerable maxim “primum non nocere”: first do not harm. (43) So, we were left with one choice: to carry out an observational study in which patients were offered the best management, from our point of view, and make the results available to others for comparisons.
References:


