The Influence of Acute Phase Blood Pressure on Stroke Outcome: To Treat Or Not To Treat?

Szőcs Ildikó[1,2], Bereczki D[4], Orbán-Kis K[1,2], Szász JA[2,3], Győri LF[5,6], Szatmári Sz[2,3]

[1] Department of Physiology, University of Medicine and Pharmacy, Tîrgu Mureş, Romania
[2] 2nd Clinic of Neurology, County Emergency Clinical Hospital, Tîrgu Mureş, Romania
[3] Department of Neurology, University of Medicine and Pharmacy, Tîrgu Mureş, Romania
[4] Department of Neurology, Semmelweis University, Budapest, Hungary
[5] 1st Clinic of Cardiology, County Emergency Clinical Hospital, Tîrgu Mureş, Romania
[6] Department of Cardiology, University of Medicine and Pharmacy, Tîrgu Mureş, Romania

Romania ranks third in stroke mortality among countries reporting vascular statistics. Acute phase blood pressure has a major influence on stroke outcome. This review aims to give an overview of available data regarding the prevalence of extreme (both low and high) values of blood pressure in acute phase of stroke, impact of blood pressure on stroke prognosis, recommendations on the management of blood pressure, available national data, large ongoing internationl trials with possible impact on stroke guidelines.
The consensus of the EUSI panel is that "emergency administration of antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg. The panel remains concerned by the evidence that aggressive lowering of blood pressure among patients may cause neurological worsening, and the goal is to avoid overtreating patients with stroke until definitive data are available".

Keywords: stroke, blood pressure, outcome, acute phase management

Introduction

Despite the considerable efforts of those who take an active part in health improvement, the problem of stroke remains very important for the next decades in Romania [1,2,3]. In the last 30 years Eastern European countries reported stroke statistics showing an important disadvantage when compared to the West, although an evident decrease of cerebrovascular mortality was seen in the last 15 years in this region [4–9]. According to the last updated statistics of the American Heart Association, Romania ranks third in stroke mortality worldwide among countries reporting vascular statistics [10].

A better management of risk factors has obviously a positive effect as it was already demonstrated in Western and Eastern countries [11–14]. International stroke guidelines are well-known to Romanian neurologists, and local health policy makers command the use of updated, adapted versions but their implementation to everyday practice and the results seem to come through quite slowly [15,16].

One of the major factors leading to stroke is hypertension and acute phase blood pressure (BP) also influences stroke outcome [17].

This review aims to give an overview of available data regarding the prevalence of extreme (both low and high) values of blood pressure in acute phase of stroke, impact of blood pressure on stroke prognosis, recommendations on the management of blood pressure, available national data, large ongoing internationl trials with possible impact on stroke guidelines, respectively.

Correspondence to Ildikó Szőcs
Email: szocsiko@yahoo.com

What impact does high BP have on stroke outcome?

Data regarding the impact of BP on stroke prognosis that are currently available are somewhat contradictory, epidemiological data on the prevalence of high BP in acute phase of stroke are abundant [7,13]. At stroke onset 60–75% of stroke patients present with elevated BP (>160 mmHg), 25-28% of them showing markedly high BP (>180 mmHg). It is known that 50% to 60% of these patients have had high BP prior to the stroke [17,18].

Only a few systematic overviews of the completed studies are at hand to enlighten the possible effects on prognosis regarding admission BP. Willmot et al perfomed a metaanalysis in 2004 concluding that high BP in acute phase of stroke is associated with poor prognosis [18]. High variability of BP is also associated with poor outcome [19]. As to the International Stroke Trial enrolling over 17.000 patients, BP has a "U-shaped" effect on stroke prognosis (both very low and high BP in the acute phase being associated with high mortality and more severe grade of dependence) [17]. A recent metaregression including 37 trials, involving over 9000 patients with acute stroke concludes that a U- or J-shaped curve was present for the relationship between outcome and systolic BP (for each of early death, end-of-trial death, and end-of-trial death or dependency). Both large reductions and any increase in BP were associated with a worse outcome [20]. They emphasize the need for large, randomized, controlled trials to support these findings.

What presumptions do we have about BP in stroke?

There are several theoretical reasons against acute treatment of hypertension immediately post-stroke:

- spontaneous reduction of BP levels over 4-10 days was recorded;
- association of acute phase high BP with favourable outcome;
- cerebrovascular reactivity is already impaired following acute stroke even without interventions and cerebral blood flow becomes dependent on systemic BP levels, its lowering being harmful on the ischemic penumbra;
- dysfunctional autonomic nervous system control of the cardiovascular system following acute stroke;
- each 10 mmHg SBP fall below 150 mmHg could lead to a 17.9% increase in early death and to an excess of coronary heart disease death [21–25].

The theoretical reasons that support acute treatment of hypertension immediately post-stroke are also substantial:

- sustained high BP may increase the brain edema [21];
- it was supposed to increase likelihood of haemorrhagic transformation of the infarct and this likelihood is still in the general thinking, although it was proved not to increase risk of hemorrhagic transformation [17];
- high BP is associated with a high risk of early recurrence (<2 weeks, every 10 mmHg over 150 mmHg being associated with 4.2% increase) and poor outcome [11,12,26,27];
- high BP in hemorrhagic stroke may contribute to extension of hemorrhage [28].

What should we do and what is done? (Guidelines and some international data on their implementation)

In view of the above mentioned high prevalence, it is surprising to encounter the international lack of consensus evident on examining treatment practices.

Data of the Stroke Association show that in the United Kingdom, 6% of physicians would start antihypertensive treatment immediately on admission for stroke, 21% would wait a few hours, 73% would wait from days to weeks [29]. In the United States of America, 57% of stroke patients received antihypertensive therapy following admission (pre-admission drugs continued in 54.5%, the rest had therapy introduced de novo, even with a very high variability in the thresholds used to intervene (University Health Consortium Stroke Benchmarking Project) [30]. According to a survey performed in two major teaching hospitals from Pakistan, 58.6% of the physicians would vigorously treat BP of 180/100 mmHg in the first three hours after ischemic stroke onset. When concerning the first 24 hours, 60% would favour lowering the same BP value [31].

The latest EUSI guidelines state that "emergency administration of antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg" [16]. These are in line with the US recommendations [32]. When pharmaceutical treatment of acute phase BP in stroke is concerned, guidelines lack details and seem inconsistent, based more on individual case reports and on theoretical arguments, and not on systematic overviews or large interventional trials. As to the guidelines, acute lowering of BP should be delayed for several days or even weeks unless thrombolysis is initiated or life-threatening conditions are present (e.g. hypertensive encephalopathy, aortic dissection, cardiac ischemia, pulmonary edema, pre-eclampsia/eclampsia or acute renal failure) [16]. Cochrane Collaboration Stroke Reviews conclude that "it remains unclear whether high BP should, or should not, be altered therapeutically during the acute phase of stroke" [33].

Until the emergence of new data, several questions about the management of arterial hypertension in the setting of acute stroke remain unanswered. What level of blood pressure would indicate initiation of new antihypertensive treatment? Which drug should be administered in this situation? Should patients previously taking antihypertensive medications continue taking them during the first hours after stroke or should new antihypertensive agents be started? Since the publication of the last guidelines, several clinical studies have provided additional information, but unfortunately definite answers to these questions are not yet available.

Ongoing international trials on modifying BP in acute phase of stroke

As to the International Stroke Trials Registry [34,35], there are many stroke trials with BP modifying interventions currently ongoing or recently stopped, but only three ongoing or recently finished have the study size and statistical power large enough to have an impact on stroke guidelines: Efficacy of Nitric Oxide in Stroke Trial, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2, and Scandinavian Candesartan Acute Stroke Trial.

The results of the Scandinavian Candesartan Acute Stroke Trial (SCAST) have been recently published, stating that "there was no indication that careful blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan is beneficial in patients with acute stroke and raised blood pressure" [36].

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT-2) is designed to assess the effect of intensive blood-pressure-lowering (within 6 h after onset) on functional outcome of acute haemorrhagic stroke patients with coexisting high (150–220 mm Hg) systolic blood pressure in 2800 participants (over 1,600 patients included until March 2011) [34,37].

Another large ongoing trial (Efficacy of Nitric Oxide in Stroke Trial, ENOS) aims to study the effect on functional outcome of lowering blood pressure with the nitric oxide donor glyceryl trinitrate, and continuing or stopping antihypertensive drugs that were prescribed before stroke in patients with acute ischemic or hemorrhagic stroke. ENOS aims to enroll up to 3,500–5,000 patients until 2013 (2,295 patients having been enrolled so far, 27 April 2011) [38].

Some data on management of BP in Romanian centres

Since treatment trends seem contradictory worldwide, it raised our interest in finding out more about our own treatment practices. Few Romanian studies have reported regional stroke statistics. Unfortunately very few large studies exploring the relationship between stroke and BP are available in Romania, even fewer are those prospective studies dealing with prognostic effects of BP alteration on stroke.

A recent anatomo-clinical statistical study performed on over 3,000 patients in 10 years shows that high blood pressure continues to influence most profoundly the incidence of stroke in Romania, high blood pressure being also the most frequent risk factor of ischemic stroke recurrence [1]. A significant percent of patients are diagnosed with high blood pressure only after onset of stroke [39]. In as much as half of the cases the secondary prevention (including treatment of high BP) is lacking completely in post-stroke patients [40]. Several studies give details on the correlation between stroke subtypes and high BP [41,42]. Few are the studies assessing treatment trends, although clinical experience shows frequent use — or abuse — of antihypertensives in the acute phase. Significant part of patients receives BP lowering agents immediately after stroke onset, even more in the first 24 hours [43]. None of the above mentioned studies assess the effect of altering BP in the acute phase of stroke on prognosis.

We have found three Romanian studies on BP and stroke outcome. One of them has included only 56 stroke patients, assessing the effect of different BP levels and of their treatment on outcome after two months, concluding that it is beneficial to lower BP moderately at stroke onset [44]. The other two studies — performed on over 100 stroke patients each — have evaluated in acute phase two treatment groups with continued and discontinued antihypertensives and found no difference in immediate outcome [45,46].

The MUD (Mures-Uzhgorod-Debrecen) study was a non-interventional, prospective study with 5-year follow-up in a group of over 400 stroke patients in the Mures patients [47,48]. We've found that low early BP (<140 mmHg) was associated with poor prognosis both in short- and in long-term, without being influenced by BP variability during hospitalization; and increase or no change in markedly high early BP was associated with poor long-term outcome; modest lowering of high early BP might be beneficial on survival [49].

Local clinical experience shows that a significant number of stroke patients receive BP lowering agents probably without justification, sometimes even before being examined by a neurologist and sometimes by neurologists who are concerned and maybe afraid of leaving high BP untreated. For certain conditions there aren't any recommendations accessible, but for some frequent conditions there are clear indications at hand [16,32,50]. It is of paramount importance to respect the available guidelines, as lacking as they may be.

What about low BP in stroke?

Data on prevalence of low BP in acute phase of stroke are even scarcer. There are some data showing a prevalence of 18–25% of lower BP than 140 mmHg in acute phase of stroke. It might be caused by hypovolemia; heart failure, myocardial infarction, cardiac arrhythmias; aortic dissection; sepsis and a certain part are surely iatrogenic due to administration of blood pressure lowering agents. This raises the possibility that at least these last cases could be positively influenced.

Guidelines recommend that causes of hypotension in the setting of acute stroke should be sought in order to correct reversible causes, such as hypovolemia and cardiac arrhythmias. Correction of hypovolemia and optimization of cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement with normal saline and correction of cardiac arrhythmias, such as slowing a ventricular response to rapid atrial fibrillation. If these measures are ineffective, vasopressor agents such as dopamine may be used.

Low BP in acute phase of stroke is also associated with poor prognosis [17]. Castillo et al noted that the rates of neurological worsening, poor neurological outcomes, or death increased when the baseline systolic blood pressure was <100 mm Hg or the diastolic blood pressure was <70 mm Hg [27].

Conclusions

Having to deal with the burden of not being able to help the patient we turn to measures that are supposed to help the patient but might prove harmful in the future. We will probably go on acting like this until stroke guidelines will be developed to standardize BP management in acute phase of stroke.

Taking part in stroke trials might have a positive effect on exploring our own treatment routines applied above and beyond guidelines. Dealing with trial patients and performing the above mentioned non-interventional regional stroke study has surely made us more aware of the measures we tend to apply routinely in spite of or in line with the recommendations. Administering antihypertensives might be considerably more frequently done than giving other drugs that are already proved inefficient, or drugs having so called neurotrophic effects. We do this in spite the lack of substantial evidence on the positive effect of BP lowering agents on stroke outcome and in spite of a mounting mass of evidence supporting injurious consequences of high BP variability.

Pending more data and consequently a new and detailed guideline on management of blood pressure in acute phase of stroke, the consensus of the EUSI panel is that "emergency administration of antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg. The panel recognizes that no data show that these values are especially dangerous and emergency treatment

is needed. However, the panel remains concerned by the evidence that aggressive lowering of blood pressure among patients may cause neurological worsening, and the goal is to avoid overtreating patients with stroke until definitive data are available" [16].

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