Elevated Blood Pressure in Acute Ischemic Stroke – Treat or Leave?

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High blood pressure (BP) levels ($>140/90$ mm Hg) are observed in a large proportion of acute ischemic stroke (AIS) patients during the early phase [1, 2]. The mechanisms implicated for elevated BP include pre-existing hypertension, activation of neuro-endocrine systems, stress of hospitalisation, infarct topography, stroke subtype, stroke severity and raised intracranial pressure [3]. Despite its high prevalence, the optimal management of BP during the early phase remains a debatable issue with little consensus.

In the natural course of AIS, the BP values tend to normalize spontaneously within hours or days after AIS onset [4]. Furthermore, since the rescue of tissue at-risk remains the main goal of AIS treatment, keeping the tissue perfusion pressure above a critical level within the ischemic penumbra remains crucial. It is well known that cerebral autoregulation normally maintains perfusion over a wide range of BP and it is set towards higher BP values in chronic hypertensive individuals. During the acute phase of IS, cerebral autoregulation becomes dysfunctional and perfusion tends to be passively dependent on perfusion pressure [5]. Hence, it has been argued that BP should not be actively lowered in order to avoid any further reduction of the CBF, with the possibility of infarct extension and worsened outcome.

Elevated BP is associated with higher rates of cerebral edema formation, death or dependency and hence, early intensive treatment has been advocated [4]. Interestingly, higher systolic BP was found to be associated with poor rates of recanalisation with intravenous thrombolysis (OR per 10 mm Hg increase: 0.85, 95% CI 0.74–0.98, $p = 0.022$) [6].

It is hypothesized that intensive BP lowering during the early period may reduce the risk of symptomatic intracranial hemorrhage (SICH) after systemic thrombolysis. While elevated BP is positively associated with poor outcome, very low BP levels (systolic <130 mm Hg) and large reductions in BP are also related to poor outcome in AIS [7]. The observed U- or J-shaped relationship of BP and outcome may be related to the overwhelming autonomic response in patients with severe AIS that often present with higher BP at presentation.

In the original National Institute of Neurological Disorders and Stroke, antihypertensive therapy was used in the placebo as well as active group. However, no conclusions could be drawn due to the small sample size [8]. Subsequent non-randomised studies indicated that elevated BP in thrombolysed AIS patients was associated with a higher likelihood of SICH. Accordingly, the Safe Implementation of Thrombolysis in Stroke-Monitoring

Study (SITS-MOST) [9], elevated baseline systolic BP was associated with SICH (OR 1.3, 95% CI 1.1–1.7 per 20 mm Hg). Similarly, the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) [10] showed a higher SICH rate and worse outcome in patients with elevated systolic BP. Interestingly, a U-shaped relationship was noted between systolic BP and death and dependency, with the best outcome observed in the nadir 141–150 mm Hg.

Current data indicate that a ≥ 15 mm Hg difference in systolic BP levels equates to about 15% reduction in a poor outcome after intravenous thrombolysis. However, the expert-derived recommendations are based mainly on the perceived harm from high BP, and a definitive study for determining the optimal BP target in AIS is warranted.

The recent meta-analysis by Liu et al. [11] showed that early BP lowering after AIS did not significantly affect the risk of early and long-term death, early and long-term dependency, early and long-term death or dependency, long-term stroke recurrence, long-term myocardial infarction, and long-term vascular events. However, the included studies were limited by the late recruitment (many

hours after stroke onset) and smaller BP difference between the active and control arms. Perhaps some definitive answers about the role of early intensive BP control in AIS might be obtained from the ongoing Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial [12]. The ENCHANTED trial is an independent, 2×2 quasi-factorial, active-comparison, prospective, randomised, open blinded endpoint, clinical trial that is evaluating tissue plasminogen activator dose and/or BP-lowering treatment initiated during the first 6-hour. Patients are randomized to the guideline-based BP levels ($<180/105$ mm Hg) or early intensive therapy arm (systolic target 130–140 mm Hg). In the meantime, any potential benefits of rapid BP lowering in AIS must be balanced against potential risks of worsening ischaemia from altered autoregulation and/or perfusion within the ischaemic penumbra.

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