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BLOOD PRESSURE TARGETS IN ACUTE INTRACEREBRAL HEMORRHAGE

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Intracerebral hemorrhage (ICH) is a major health care problem with an incidence of 24.6 per 100.000 person-years [1]. It represents 10 to 20% of all strokes in Caucasians and is associated with poor prognosis [1,2]. The case-fatality rate of ICH is high and ranges from 40% at 1 month to 55% at 1 year [1]. In addition, survivors of ICH have often severe disability, with only 18 to 39% of patients living independently at 1 year [1]. Treatment strategies, such as surgical hematoma evacuation and recombinant Factor VII, have failed to improve outcome and reduce mortality in patients with ICH. Currently, management of ICH consists mainly of supportive therapies in intensive care units. The early management of blood pressure (BP) in acute ICH is a challenging therapeutic option, despite the controversial results from randomized clinical trials.

It is well known, that BP during the acute phase of ICH is elevated (>140/90 mmHg) in approximately 75% of patients [3]. A number of factors, such as autonomic dysfunction, activation of the neuroendocrine system, recent premorbid BP increase, pain, stress and Cushing reflex, have been proposed as possible mechanisms for post-ICH severe hypertension [4]. Most observational studies have illustrated that elevated BP is associated with increased risk of death, disability or neurological deterioration in patients with acute hemorrhagic stroke [5,6]. In addition, some studies have demonstrated that increased BP is related to hematoma growth and formation of cerebral edema [7,8]. Hematoma expansion is a frequent complication of ICH, occurring in 30% of patients with hemorrhagic stroke, whilst one-third of them develop the expansion within 3 hours of ictus [9]. Several studies have reported that hematoma enlargement is associated with neurological deterioration and poor outcome [10,11]. Hematoma volumes greater than 30 ml are related to increased mortality rates (60%-90%) at 1 month after ICH [12]. Moreover, the INTERACT1 study revealed that for each 1 ml increase in hematoma expansion, the risk of death and dependency will increase by 5% [13]. Hence, this has prompted some researchers to conclude that hematoma growth might be the biological link between elevated BP and mortality. Furthermore, the possible benefits of early BP lowering treatment on hematoma enlargement and outcome in acute ICH patients, has led to the conduction of randomized clinical trials in order to determine the safety and efficacy of early BP management on hematoma expansion, mortality and disability.

Early intensive BP reduction in acute ICH – pilot trials

The safety and feasibility of intensive BP lowering treatment in patients with acute hemorrhagic stroke was investigated by two pilot, prospective, randomized trials, which were used as a run-in phase to larger trials. The INTERACT1 (INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial) was an international, open-label, blinded end-point trial, which enrolled 404 patients with acute ICH and elevated systolic BP (SBP) levels (150-220 mmHg) within 6 hours of onset and randomized them to either intensive BP treatment (SBP target <140 mmHg within 1 hour of randomization and maintaining it for the next 7 days) or guideline-based management of BP (SBP target <180 mmHg) [14]. The choice of antihypertensive treatment was determined by the investigator's preference. The aim of the study was to assess safety, efficacy (proportional change in hematoma volume at 24-h) and clinical outcomes (death or disability) of treatment at 90 days. The mean SBP difference between the groups was 13.3 mmHg ($p<0.0001$) at 1 hour from randomization, however, the prespecified SBP target at 1 hour was achieved in only 40% of patients randomized to the intensive BP lowering arm. The rates of serious adverse events, neurological deterioration and poor clinical outcome did not differ significantly between the two groups. Furthermore, intensive BP reduction attenuated proportional hematoma growth at 24 hours, not significantly though ($p=0.06$).

Cerebral Hemorrhage) study, 60 patients with acute hemorrhagic stroke and SBP>170 mmHg were randomized, within 6 hours of symptom onset, into one of three SBP target levels: 170-199, 140-169 and 110-139 mmHg [15]. Patients were treated with intravenous nicardipine for achieving and maintaining BP goals for 24 hours. The study aimed to determine feasibility, safety (neurological deterioration at 24-h and serious adverse events at 72-h) and efficacy (disability or death at 90 days) of intensive BP reduction. Although SBP values were significantly different among the tiers, treatment failure was observed in 9 of 60 subjects, all in the lowest SBP level. The mortality at 3 months was lower than expected in all SBP levels and the rates of serious adverse events and neurological deterioration were below the prespecified safety thresholds. A post-hoc analysis of ATACH1 trial didn't reveal any significant associations between different SBP levels and hematoma expansion [16].

Both pilot trials demonstrated that intensive BP lowering in the setting of acute ICH is safe and feasible and may be associated with reduced hematoma growth. However, the opponents of this treatment strategy are concerned that the already compromised cerebral blood flow (CBF) in the perihematomal area due to the compression of small arteries by the hematoma and the associated edema will be further reduced by aggressive BP lessening and might led to perihematomal ischemia. The ICH-ADAPT (the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial) assessed the impact of aggressive BP lowering on CBF and provided strong arguments against this hazard [17]. A total of 75 patients with acute hemorrhagic stroke and SBP>150 mmHg were randomly assigned within 24-h of onset to a SBP goal of less than 150 mmHg or less than 180 mmHg. The SBP target had to be achieved within 1 hour from randomization by means of intravenous antihypertensive treatment. The aim of the study was to investigate the effect of intensive vs standard BP lowering treatment on perihematomal CBF, which was measured by performing computed tomography perfusion imaging at 2 hours post-randomization in both groups. At the time of the computed tomography perfusion scan, the mean SBP in the intensive and guideline-recommended treatment groups were 140 and 162 mmHg, respectively. Treatment failure occurred in 21% of patients of the intensive target group. The results showed that intensive BP treatment was not associated with impairment of perihematomal CBF compared to the standard treatment group and does not induce cerebral ischemia in ICH patients. Moreover, a post-hoc analysis of ICH-ADAPT reported that early aggressive BP lowering was not associated with perihematomal edema growth [18]. This finding further supports the safety of early BP lowering in acute ICH. However, it also indicates that intensive BP treatment has no effect on perihematomal edema attenuation.

Early intensive BP reduction in acute ICH – randomized clinical trials

The promising observations, regarding safety and feasibility, from INTERACT1 and ATACH1 studies has led to the conduction of two large randomized clinical trials, which aimed to investigate the impact of early aggressive BP lowering on clinical outcome in ICH patients.

INTERACT2 was an international, prospective, randomized, open-label, blinded end-point trial [19]. The study randomized 2839 ICH patients with SBP levels between 150 and 200 mmHg within 6-h of onset to an intensive (SBP<140mmHg, achieved within 1 hour and maintained for 7 days) or a guideline-recommended SBP target (SBP<180mmHg). The choice of antihypertensive treatment was based on the local availability of agents. The composite primary outcome of the study was death or major disability, defined as a modified Rankin Scale (mRS) score of 3 to 6 at 90 days, whilst the secondary outcomes included ordinal analysis of the primary endpoint, all-cause mortality, health-related quality of life, duration of hospitalization, living

serious adverse events. The intensive treatment group presented significantly lower SBP than the guideline treatment group from 15min to day 7, with a mean difference of 14mmHg at 1 hour after randomization (p<0.001). At 3 months, the rates of death and severe disability didn't differ significantly between the two groups, although the primary outcome was reduced by 25% in the intensive compared to the guideline treatment group (OR 0.87; 95%CI=0.75-1.01; p=0.06). The effects of intensive BP control on the primary outcome were consistent across all prespecified subgroups. However, ordinal analysis demonstrated a significantly favorable functional outcome in intensive treatment groups patients compared to their counterparts (OR 0.87; 95%CI=0.77-1.00; p=0.04). Furthermore, intensive BP treatment was safe and associated with significantly better health-related quality of life than standard BP treatment. In contrast, the two groups did not differ significantly in terms of all-cause mortality and hematoma expansion.

The INTERACT2 study failed to demonstrate the superiority of intensive BP lowering treatment on the primary endpoint and the hematoma growth. The neutral results of the study could be attributed to the following issues: 1) a sub-analysis of INTERACT2 showed that SBP values greater than 130 – 140 mmHg in the hyperacute and acute phase of hemorrhagic stroke are associated linearly with increased risk of physical dysfunction [20]. Moreover, another sub-study of INTERACT2 reported that the attenuation of hematoma expansion was greater among patients who achieved greater BP reductions (>20mmHg) within 1 hour of treatment initiation [21]. However, the prespecified BP target of less than 140mmHg within 1 hour was not achieved in 66% of patients in the intensive BP lowering group. The increased rates of treatment failure may have influenced the outcome of the study. 2) The baseline hematoma volumes in INTERACT2 were small (median volume 11ml). It is well known that the risk for hematoma expansion depends on the initial hematoma volume and that small hematomas are less likely to expand and are associated with more favorable outcome compared to larger hematoma volumes [22]. Indeed, the low mortality rates (12%) in both arms of INTERACT2 may reflects the better clinical outcome related to small hematoma volumes. 3) A post-hoc analysis of INTERACT2 illustrated that SBP variability and maximum SBP, during the hyperacute and acute phase of ICH, were strongly associated with poor outcome at 90 days independently of SBP levels [23]. Therefore, efforts should be taken to ensure not only BP goal achievement, but also the stability and consistency in BP reduction in patients with acute ICH. 4) Finally, In INTERACTs studies the choice of antihypertensive treatment depended on availability and the investigator's preference. The study population was treated with various antihypertensive agents that may have limited antihypertensive efficacy (furosemide), decrease cerebral perfusion pressure (sodium nitroprusside) or have no effect on BP variability.

The ATACH2 trial was a multicenter, open-label trial, blinded endpoint, which randomly allocated 1000 patients with acute ICH (hematoma volume<60ml) and increased SBP levels >180 mmHg to an aggressive SBP target (110-139mmHg) or a standard SBP target (140-179 mmHg) within 4.5 hours of symptom onset by means of intravenous nicardipine [24]. The trial was designed to evaluate the potential benefits obtained with tight compared to standard SBP targets on the primary (death or severe disability (mRS>3) at 3 months) and secondary outcome measures (all-cause mortality, health-related quality of life, hematoma growth, neurological deterioration and serious adverse events). During the first 2 hours after intervention, the mean minimum SBP for intensive and standard treatment groups were 129 and 141 mmHg, respectively. The treatment failure at 2 hours after randomization was 12.2% in the intensive group and 0.8% in the standard group. However, the two groups did not differ significantly regarding the primary and secondary outcomes of the study. The prespecified subgroup analysis revealed non-significant differences regarding the primary outcome of the study. Aggressive treatment group demonstrated non-significantly lower rates of hematoma growth (p=0.09). Moreover, patients in the intensive group presented borderline significantly increased rates of any serious adverse events at 3 months (p=0.05) and significantly higher rates of renal adverse events at 7 days after randomization (p=0.002) compared to the standard group. Thus, the results of ATACH2 trial suggest that aggressive BP lowering treatment in acute ICH is not effective and potentially harmful.

Early intensive BP reduction in acute ICH – meta-analysis

Currently, three meta-analyses have assessed the safety and efficacy of intensive compared to standard BP lowering in acute ICH. However, none of them had included the recently published ATACH2 in their analysis. A meta-analysis of four randomized controlled trials, including 3.135 ICH patients showed that intensive BP reduction is safe [25]. The allocation of ICH patients to a tight versus guideline-recommended BP control was associated with a non-statistically significant trend toward better functional outcome at 3 months. Moreover, Tsivgoulis et al demonstrated that intensive BP lowering was related to a greater attenuation of absolute hematoma growth at 24 hours. Another meta-analysis of 3.000 ICH patients from seven prospective randomized trials confirmed the findings of Tsivgoulis et al, regarding safety and functional outcome [26]. However, aggressive BP lowering was not associated with reduction of hematoma expansion. Finally, meta-analysis of four randomized trials with 1.427 patients, conducted by Pan et al, illustrated that intensive BP lowering in patients with acute hemorrhagic stroke is safe and may improves functional outcome and attenuate hematoma enlargement [27].

Guidelines and perspectives

The novel findings of randomized controlled trials (INTERACT1, ATACH1, INTERACT2 and ICH-ADAPT) have influenced the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization (ESO) and forced them to modify the previously published recommendations on BP management in acute hemorrhagic stroke. Currently, the AHA/ASA guidelines, published in 2015, for the management of spontaneous intracerebral hemorrhage recommend that for ICH patients with elevated SBP between 150 and 220 mmHg, early SBP lowering to 140 mmHg is safe (Class I; Level of Evidence A) and may improve functional outcome (Class IIa; Level of Evidence B) [28]. In a similar way, the ESO guidelines, published in 2014, state that in patients with acute ICH, early (within 6 hours of onset) aggressive BP lowering (SBP< 140mmHg within 1 hour of treatment initiation) is safe and may be superior to a less tight SBP target (>140mmHg) [29]. Furthermore, all meta-analyses have confirmed guidelines recommendations, demonstrating that intensive BP lowering in acute ICH is safe and may improve functional outcome and hematoma expansion. However, the recently published ATACH2 study, which was not included in the meta-analyses, does not support an aggressive SBP control in the setting of ICH. The results of ATACH2 study have dampened the enthusiasm of early aggressive BP lowering in these patients, in terms of safety and efficacy. Thus, further randomized controlled studies are needed to define the optimal BP management in the acute phase of hemorrhagic stroke. Until then, the BP goal in acute ICH will remain a matter of considerable debate.

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