Selected Summaries

Intensive lowering of blood pressure in acute intracerebral haemorrhage: Where do we stand today?

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SUMMARY

Qureshi *et al*. contribute a valuable randomized controlled study that defines the safety and efficacy of rapid and hyperacute lowering of blood pressure (BP) versus cautious and less intensive reduction in BP following acute intracerebral haemorrhage (ICH). In this study, 1000 patients with a spontaneous ICH were randomized within 4.5 hours of onset of symptoms to standard care (systolic BP [SBP] target of 140–179 mmHg) or intensive BP control (SBP target of 110–139 mmHg) to test the superiority of intensive reduction of SBP to standard reduction. The exclusion criteria included a Glasgow Coma Scale score of 3–5, a structural cerebral cause of the haemorrhage, a massive haematoma with a poor prognosis, or a planned early surgery. The primary outcome was death or disability (modified Rankin scale score of 4–6) at 3 months after randomization, as ascertained by an investigator who was unaware of the treatment assignments.

The mean (SD) minimum SBP during the first 24 hours was 128.9 (16) mmHg in the intensive treatment group and 141.1 (14.8) mmHg in the standard treatment group. The antihypertensive regimen was intravenous nicardipine at a dose of 5 mg per hour, increased up to a maximum of 15 mg per hour. If the target SBP was not reached over 30 minutes, a second agent such as either intravenous labetolol, diltiazem or urapidil was used. The primary outcome of death or disability was observed in 38.7% of patients in the intensive treatment group and in 37.7% in the standard treatment group. Serious adverse events occurring within 72 hours after randomization, which were considered by the site investigators to be related to the treatment, were reported in 1.6% of patients in the intensive treatment group and in 1.2% of those in the standard treatment group. The rate of renal adverse events within 7 days of randomization was significantly higher in the intensive treatment group than in the standard treatment group.

The authors concluded that the results do not support the belief that acute reduction of SBP to a target of 110–139 mmHg in patients with acute ICH is more effective in improving functional outcome than a less aggressive reduction to a target SBP of 140–179 mmHg.

COMMENT

Elevated BP is common in acute ICH because of a variety of factors, including stress, pain, increased intracranial pressure (ICP), and premorbid acute or persistent elevation of BP. Although there is a clear relationship between chronic hypertension and ICH, the relationship between acute elevation of BP and ICH remains unclear. Even with the recent randomized controlled trials, no clear clinical guidelines can be made. The impact on outcome and relationship with lowering of BP vary across studies. The major rationale for lowering BP acutely is that early rebleeding or progression of size of haematoma may be important causes of morbidity and death, and rebleeding may be related to acute or chronic hypertension.[1–5]

The pathophysiology of ICH is complex. A definite physical disruption is caused by the haematoma. However, local tissue pressure produces a zone of ischaemia surrounding the clot and cerebral blood flow (CBF) in this region which may be close to or below the levels required to maintain neuronal viability. The clot is a space-occupying lesion that often leads to an increase in local ICP. Generalized increases in ICP may further impair cerebral perfusion pressure (CPP) and CBF both locally and in more distant sites. Animal models have shown both impaired autoregulation and decreased CBF following ICH. As with acute ischaemic stroke, there is a scientific basis for believing that reductions in arterial pressure will further impair CBF and lead to worsening of the ischaemic damage. These reasons lead us to assume that any decease in systemic BP will compromise cerebral perfusion and that treatment should be aimed at decreasing ICP rather than reducing systemic BP directly.[1,5]

Whether or not and how aggressively to treat elevated BP in the face of acute ICH are questions stroke neurologists and hypertension experts have been debating for decades. Whether the elevated BP after acute ICH is simply a marker of increased ICP and a poor prognosis or a potential target for intervention is unknown.

The 2010 guidelines from the American Stroke Association (ASA) suggest aggressive treatment of BP in patients with acute ICH with intravenous antihypertensive agents if:[6]

1. The SBP is >200 mmHg or the mean arterial pressure (MAP) is >150 mmHg.
2. The SBP is >180 mmHg or MAP is >130 mmHg and there is suspicion of increased ICP.
3. Modest reduction of BP is suggested in patients with SBP >180 mmHg or MAP >130 mmHg if there is no evidence of increased ICP.
4. Careful and near continuous monitoring in patients with acute ICH on antihypertensive therapy to assess for worsening of neurological status or drop in CPP.

Each of these recommendations has a level of evidence C, which indicates opinion because there is a lack of well-designed clinical trials.

On the basis of the results of a pilot study (The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial [INTERACT-1]),[2] investigators developed and executed an international clinical trial known as INTERACT-2 to determine the safety and efficacy of early, intensive lowering of BP in patients with acute ICH. INTERACT-2 assigned 2839 patients with a mean age of 63.5 years from 21 countries to receive intensive treatment to lower their SBP to a target level of <140 mmHg within 1 hour and be maintained for at least 7 days or to a less intensive SBP target level of <180 mmHg, closer to the current standard of care. After 90 days of follow-up, intensive treatment of BP led to no significant improvement in the primary outcome, death or disability. No significant difference was seen on follow-up imaging in the volume of haematoma and importantly no increase was noted in treatment-related adverse events in the intensively managed group. While there was no clear advantage in the primary end-point, the intensively treated group did show significantly lower Rankin scores, a pre-specified secondary end-point, suggesting a better functional status. Subgroup analysis did not show enhanced clinical benefit or harm in any particular group. While the results of INTERACT-2 did not support treating patients with acute ICH to a more aggressive goal of BP, the lack of harm in the intensively treated group and improvement in the secondary end-point of functional outcome suggest enough clinical equipoise to study this question further.[2]

Following the results of INTERACT-2, the guidelines have been modified recently.[7] For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (Class II; level of evidence A) and can be effective for improving functional outcome (Class IIa; level of evidence B). This statement has been revised from the previous guideline.

For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (class IIb; level of evidence C). This statement is also a new recommendation.

The recently published ATACH-2 trial results threw up more dilemmas than clarifying nebulous issues.

The ATACH-2 trial was discontinued for futility before it reached the target enrolment of 1280 participants. The reported results are at variance with what was reported by INTERACT-2. There were several key differences between both these trials. Nearly 41% of the participants in the INTERACT-2 trial underwent randomization after 4 or more hours of onset of symptoms whereas all participants in the ATACH-2 trial underwent randomization and were treated within 4.5 hours of the onset of symptoms. In INTERACT-2, only 48% of the 2839 participants underwent randomization with an SBP of ≥180 mmHg, whereas all the participants in ATACH-2 had an initial SBP of ≥180 mmHg. Primary treatment failure was seen in 66% of participants within 1 hour of randomization in INTERACT-2 and in 12.2% of those in the intensive treatment group within 2 hours of randomization in the ATACH-2 trial. Also the mean SBP in the first 2 hours after randomization was 128.9 mmHg and 150 mmHg, respectively in ATACH-2 and INTERACT-2 trials. Therefore, the postulation that a more rapid and intensive reduction in SBP than that used in INTERACT-2 may show a larger magnitude of therapeutic benefit proved false.

The lack of an incremental clinical benefit on intensive reduction of the SBP is difficult to explain. As the authors suggest, it is possible that the blunting of fluctuations in SBP in patients with ICH and an acute hypertensive response may exert a therapeutic benefit that is independent of the magnitude of lowering the SBP. The results of this trial also cannot be generalized to patients with large ICH, elevation of ICP or compromised CPP. Therefore, the possibility of precipitating global or regional cerebral hypo-perfusion with intensive reduction of SBP in such patients may still be a concern.

Finally, therefore, the message for the family physician will be that though the results of the INTERACT-2 trial reassured that lowering of BP in patients with acute ICH is at least not harmful, the results of the ATACH-2 trial have dampened the enthusiasm of more rigorous and hyperacute lowering of SBP in these patients. Moreover, both these trials could not document a benefit in outcome. Hence, the dilemma regarding intensive control of BP in patients with acute ICH continues for now.

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