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COMMENTARY

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Managing blood pressure in acute intracerebral hemorrhage

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1 | INTRODUCTION

Intracerebral hemorrhage (ICH) results from the rupture of cerebral vessels leading to the development of a hematoma in the brain. It comprises approximately 15%-30% of all strokes and affects more than 1 million people every year worldwide.[1] Hypertension is the most common cause of ICH, and less frequent etiologies include coagulopathies, cerebral amyloid angiopathy, vascular abnormalities, brain trauma or tumors, and infections.

Cerebral hemorrhage is the stroke subtype characterized by the highest mortality and morbidity: the fatality rate is about 40% at 1 month from bleeding and most survivors retain a severe residual disability, with only 20%-40% of patients living independently at 1 year.[2] Currently, medical and surgical strategies have substantially failed to improve outcome, and the management of ICH consists mainly of supportive therapies. The understanding of the mechanisms underlying the course of hematoma and the progression of the injury in surrounding parenchyma is, hence, of paramount relevance to identify therapeutic targets and effective treatment approaches.

2 | PRIMARY AND SECONDARY BRAIN INJURY FOLLOWING CEREBRAL HEMATOMA

Several mechanisms are involved in brain injury related to ICH. Primary brain injury, which occurs at the time of hemorrhage, is due to the mass effect caused by extravasation of blood, physical disruption of adjacent tissue and mechanical compression of local structures. The hematoma can also increase the intracranial pressure, impair cerebral blood flow, and lead to brain herniation.[3] Although damage occurring immediately after ICH is untreatable, it is worth noticing that around one third of patients undergo hematoma expansion (HE) within the first days after stroke.[4] Hematoma growth contributes to midline shift and early neurological deterioration, and is consistently associated with higher fatality and poorer clinical outcome.[5] Remarkably, the intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT-1) demonstrated that each 1 mL increase in HE is associated with a raise in the risk of death and dependency by 5%.[6]

Secondary brain injury is due either to the body and tissue response to the hematoma or to the toxic effects of clot components, and includes a cascade of events, as inflammation, iron-mediated oxidative stress, apoptosis, necrosis, and autophagy, which mainly result in the development of peri-hemorrhagic edema (PHE).[7] Cerebral edema occurs within hours of ICH, peaks several days later and can last for weeks.[5] In the hyperacute phase, PHE involves clot retraction, trans-capillary efflux of electrolytes, water and osmotically active serum proteins, and cytotoxic edema from neuronal energy failure. In the acute phase, during the first few days, PHE is sustained by coagulation cascade, thrombin production, immune reaction, and inflammatory cells.[8,9] Finally, beginning from approximately 72 hours after ICH, PHE formation involves erythrocyte lysis and hemoglobin-induced toxicity.[10] PHE may contribute to an overall increase in peri-hematoma volume by 75%,[11] and several studies associated it with an increased risk of poor outcome.[10]

3 | TARGETING BLOOD PRESSURE IN CEREBRAL HEMORRHAGE

High blood pressure (BP) during the acute phase of ICH, which is found in more than two thirds of patients, has been related to HE, PHE, and increased risk of neurological deterioration, disability, or death in most observational studies.[12]

In the current issue of *The Journal of Clinical Hypertension*, Zang et al[13] explored the effects of aggressive BP-lowering treatment on hematoma and PHE growth and functional outcome in patients with acute ICH. One-hundred and twenty-one patients with spontaneous ICH confirmed by head computed tomography and elevated

systolic BP (SBP) level (150-220 mm Hg) within 1 hour of onset were randomly assigned to early intensive or standard treatment. In both groups, 25 mg of urapidil injection was slowly administered intravenously in 6 hours from the onset; 100 mg of urapidil was further slowly administered via micropump in the intensive arm.[13] The intensive strategy resulted effective to reduce re-bleeding and perihematomal edema in comparison to control and was associated to better short-term functional outcome as assessed by National Institutes of Health Stroke Scale scores and Barthel Index up to 90 days.[13] There was no significant difference in mortality between the two groups.[13]

The current study supplies fresh insights toward the optimal treatment of high BP after ICH, which still represents one of the most debated and controversial issue in the acute stroke management. Ongoing uncertainties exist with respect to both the entity and timing of BP reduction.[14,15] In randomized controlled trials, the early intensive BP lowering (<140 mm Hg) did not demonstrate detrimental effects on the neurological status, attenuated the HE and was overall safe, but it did not significantly reduce the 3-month death or disability rate in comparison to conservative management in patients presenting with acute-onset spontaneous ICH and high BP levels.[16] Current guidelines on the management of ICH state that acute lowering of SBP to 140 mm Hg is safe (*Class I; Level of Evidence A*) and can improve functional outcome (*Class IIa; Level of Evidence B*) in patients presenting with SBP between 150 and 220 mm Hg. The aggressive reduction of BP with a continuous intravenous infusion and frequent monitoring may be also reasonably considered for ICH patients presenting with SBP > 220 mm Hg (*Class IIb; Level of Evidence C*).[17]

The debate about BP treatment may be, however, futile without taking into account a lower limit for the target range.[18] The evaluation of discrepancies between INTERACT-2 and Antihypertensive Treatment of Acute Cerebral Hemorrhage-2 (ATACH-2) trial and ad hoc analyses of INTERACT-2 data suggested a J-curve relationship, with SBP targets of 130 mm Hg the first day after ICH and 140 mm Hg the first week for optimal functional prognosis.[19-21] Indeed, the acute hypertensive response may be protective and preserve cerebral blood flow in presence of increased intracranial pressure, and overshoot may be associated with penumbral risk or circulatory insufficiency. An increased prevalence of remote cerebral ischemic lesions, neurologic deterioration during hospitalization, and longer days spent in the neuro-intensive care unit correlated with severe SBP drop and decrease in minimal SBP below 130 mm Hg, rather than average SBP achieved.[22] The increased risk of acute kidney failure with low minimum SBP suggested that aggressive BP lowering can also have the potential for end-organ harm in systemic vascular beds.[22] The threshold of 130 mm Hg could, therefore, represent a possible SBP sweet spot for either efficacy or safety.[18] Remarkably, a rightward shift of the cerebral auto-regulatory curve may occur and the lower limit of cerebral perfusion may be compensated at higher BP values in hypertensive than normotensive patients.[23] In this regard, auto-regulatory indices and neuroimaging markers of ischemic risk might be implemented in the therapeutic decision-making tree to ensure a more efficient control of BP by defining the drop in BP values that can be sustained without affecting brain metabolism, mainly in the peri-hematoma area.[24]

In addition to absolute BP levels, variability of BP values over time represents more than a confounding phenomenon,[25,26] and it has been proven to represent an independent determinant of outcome.[27-29] Recurrent sudden rises and falls in BP may promote arterial bleeding and HE, affect cerebral blood flow and favor perihematomal ischemia, contribute to disruption of the blood-brain barrier and promote vasogenic edema, and amplify cell death and secondary injury in the potentially viable area surrounding the hematoma.[30,31] Stabilization of BP variability during the hyperacute and acute phases aiming for a tight target range may represent a promising therapeutic target for future clinical trials.

4 | MULTIVARIABLE INTEGRATED MODELS IN STROKE TREATMENT AND OUTCOME PREDICTION

Expanding knowledge in the fields of either basic or clinical sciences provided evidence that effectiveness of treatments and final outcome following stroke rely on a multitude of variables, which act at the site of cerebral injury and systemic level, and include patient demographics, concomitant disease and medications, cerebral hemodynamics, inflammatory reaction, and metabolic homeostasis.[32-36] The heterogeneity of such variables and their mutual interplay offer the challenging opportunity to weight therapeutic options and appropriately select patients who could further benefit from more aggressive interventions.

The optimal management of stroke patients may, hence, lie ultimately in goal-directed strategies tailored on individual bases.[37-40] The increasing availability of electronic medical records and growing computational resources to analyze big-data are expected to allow the development of integrated models of care on the pathway of the precision medicine in the next future. Building partnerships and creating synergies across stroke centers worldwide are mandatory to expedite this process.

CONFLICT OF INTEREST

None.

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