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EDITORIAL

Intracerebral Hemorrhage: A Multimodality Approach to Improving Outcome

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Intracerebral hemorrhage (ICH) is caused by a heterogeneous group of pathologies, but its injury upon cerebral tissue arises from similar mechanisms: direct cerebral tissue destruction, hematoma expansion, mass effect, inflammation, and toxicity associated with blood components and hemoglobin metabolic products such as iron [1–8]. Primary ICH affects nearly four million individuals worldwide with 40 % of the patient unable to survive longer than 1 month [9]. Primary ICH is thought to arise from structural damage to perforating vessels leading to aneurysmal formation and subsequent rupture. Hypertension leads to degenerative changes within the vascular wall leading to vessel wall weakness and aneurysm formation while amyloid deposition within the vessel wall can lead to fibrinoid necrosis and thus subsequent vessel rupture. Most certainly, ideal treatment of any pathology lies in prevention, and thus managing hypertension is ideal in preventing ICH as well as recurrent episodes.

Hematoma expansion affects nearly 35 % of patients who present within 3 h of ictus and represents a potentially preventable mechanism of improving clinical outcome and reducing mortality [10]. Expansion of the clot seems to occur within 3 h of presentation and is potentially caused by refractory hypertension as well as coagulopathies. Two randomized control trials have shed light on treatments to address these two issues. The second of the intensive blood pressure in acute cerebral hemorrhage trial (INTERACT II) was a study which allowed patients presenting within 6 h of ICH symptomatology to be randomized to either intensive blood pressure management (systolic blood pressure (SBP) <140 mmHg) or standard treatment (SBP <180 mmHg) [11]. At 90 days, there was no significant difference in the occurrence of poor outcome between the groups: 52 % within the intensive group and 55.6 % in the standard treatment group. At 24 h post presentation, the mean hematoma growth within the intensive group was 2.5 cc as compared to 5.5 cc in the standard treatment group; however, the difference was not significant. Even though the primary outcome was not met and there was not a significant reduction in hematoma growth, a significantly higher proportion of patients within the intensive management group achieved functional outcome as compared to those in the standard management group. This phenomenon could be related to neuroprotection gained from strict SBP control as the difference would not be explained by the lack of hematoma growth differences in the two groups. This trial sheds light on the fact that strict SBP control was not detrimental and in fact may be helpful for obtaining functional outcome.

Primary ICH may be caused secondary to the use of anticoagulation therapy, and thus it is imperative that such therapy be reversed in those patients with an acute ICH in order to prevent hematoma growth as well as to allow for surgical intervention. Factor VIIa for acute hemorrhagic stroke trials (FAST trial) was evaluated by randomizing ICH patients who had presented within 6 h of ictus into three groups: control, 20 μg/kg factor VIIa, or 80 μg/kg factor VIIa. Phase II trials had shown the safety profile as well as the ability to prevent hematoma expansion. Activated factor VIIa binds to activated platelets in regions of injury and thus leads to the formation of activated thrombin and subsequent hemostasis [12]. Results of the FAST trial revealed a similar ability to reduce hematoma expansion as was observed in the phase II trial; however, there were no significant differences in mortality among the control (24 %), low-dose (26 %), and high-dose (29 %) factor VIIa patients [13]. While this trial failed to show benefit, rapid reversal of patients on anticoagulants is essential.

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Mass effect results in brain injury after ICH, but the Surgical Trial in Intracerebral Hemorrhage (STICH) trial failed to show any benefit of hematoma evacuation [14]. The role of surgery in managing ICH has been re-evaluated in the current surgical trials in lobar intracerebral hemorrhage (STICH II). Patients presenting with 10–100 cc superficial lobar hemorrhages within 48 h of ictus were randomly assigned to surgical evacuation versus best medical management [9]. The median size of hematoma evacuated was 36 cc at a depth of 1 mm, and 21 % of patients assigned to the medical management arm underwent surgical evacuation as their condition was deteriorating secondary to mass effect. The intent to treat analysis revealed a 6 % (18 vs. 24 %) advantage in mortality for the surgical population; however, the difference was not significant. Individuals in the poor prognosis group (larger hematomas and lower Glasgow coma scale scores) had a significantly more favorable outcome with surgical evacuation than medical management (p=0.02). The role of surgery may be much more favorable as the 21 % crossover from medical to surgical group, inclusion of patients with small hematomas without mass effect, and a 12 h window for performing surgical evacuation leads to diminishing returns for the surgical group. Future studies will need to evaluate the role of surgical evacuation in those with ICH-associated mass effect causing significant neurological disability.

Some have proposed that a lack of therapeutic effect seen with surgical evacuation could be associated with a normal cerebral tissue injury from surgical trauma. In addition, surgical evacuation of deep hemorrhages is not feasible as it would require traversing a significant area of normal cerebral tissue, thus minimally invasive methods are essential. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for ICH (MISTIE Trial) represents a minimally traumatic method of evacuating both superficial and deep hemorrhages. MISTIE II results have showed a significant reduction of hematoma volume as well as perihematomal edema [15]. At present, the phase III trial is recruiting patients to evaluate whether the reduction in hematoma size and edema translates to a reduced mortality and improved functional outcome.

In addition to removing the hematoma, iron chelation with deferoxamine could be a new treatment for ICH patients. It is well known that brain iron overload has a major role in ICH-induced brain damage. Deferoxamine mesylate has been shown to be safe for systemic administration in ICH patients without an increase in the rate of serious adverse events [16]. Currently, the trial to determine therapeutic benefits of systemic deferoxamine administration in ICH patients is ongoing (NCT 01662895).

ICH leads to significant mortality and morbidity secondary to a combination of mechanisms ranging from direct cerebral injury to brain edema and iron-related neuronal injury. Multiple mechanisms, including early hematoma enlargement, mass effect, and iron-induced neuronal toxicity, contribute to brain damage following ICH. We should consider trials which utilize multimodality treatments, for example, clot removal plus iron chelation, for improving ICH outcome [17–19].

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Conflict of Interest Aditya Pandey and Guohua Xi declare that they have no conflict of interest.

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