Stroke

ADVANCES IN STROKE

Neurocritical Care Updates in Cerebrovascular Disease

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Neurocritical care research has soldiered on despite disruptions in operational rhythms and intermittent pauses due to coronavirus disease 2019 (COVID-19). This article presents advances in neurocritical care pertaining to cerebrovascular disease: bedside physiological parameters, secondary injury, and neuroprotection (Figure). Given the impact of COVID-19 on the brain, a brief Data Supplement summarizes recent findings pertaining to virus/vaccine pathologies in neurocritical care units.

PHYSIOLOGICAL PARAMETERS

The quest for the ideal blood pressure (BP) in different acute neurological pathologies remains elusive. Variation exists even within individuals depending on time, host response, and spatial location relative to the site/type of primary injury. Precision cerebrovascular health—an emerging field—requires big data collection, curation, and large-scale bioinformatics. Although precision medicine has tremendous potential to improve management (particularly at extremes of the normal distribution), optimal BP targets within a disease process may be similar across a plurality of patients or subgroups.

BP After Intracerebral Hemorrhage

Results from 2 earlier landmark randomized controlled trials (RCTs) were inconsistent: although neither reported a difference between systolic BP (SBP) 110 to 139 versus 140 to 179 mm Hg, INTERACT 2 (Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) had a signal of benefit versus one of harm in ATACH2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage-II). Key differences in ethnicity, treatment duration, and achieved SBP precluded easy comparisons. The preplanned pooled analysis (n=3829) is informative.[1] Achieved SBP, variability, and magnitude of reduction were collectively associated with better safety and efficacy including hematoma expansion, neurological deterioration, functional independence, and mortality. Every 10-mm Hg reduction in SBP over 24 hours (to 120–130 mm Hg) increased favorable functional recovery odds by 10%. Smooth control was valuable. Rapid large reductions (≥60 mm Hg within 1 hour) were detrimental. Linear associations between SBP reduction and favorable outcome extended beyond 140 mm Hg with little harm. Effects of ultra-intensive reduction SBP <120 mm Hg, occurring in ≈2%, remain unclear. ADAPT-2 (phase 2, adaptive randomization, NCT02281838) comparing <140 versus <180 is recruiting.

The benefit of intensive SBP control may not extend to patients presenting with SBP ≥220 mm Hg.[2] In a post hoc analysis of ATACH2, of the 228 patients with initial SBP >220 mm Hg, intensive reduction yielded higher rates of 24-hour neurological deterioration (P=0.04) without reducing hematoma expansion. No differences were observed in 90-day death or severe disability. Although this suggests low long-term risk of intensive reduction in this subgroup, caution is warranted given the sample size and the potential for acute decline.

BP After Endovascular Treatment for Large Vessel Occlusion

Optimal BP targets post-endovascular treatment (EVT) are likely critical but remain unclear. While post-EVT hemorrhagic transformation from reperfusion injury may

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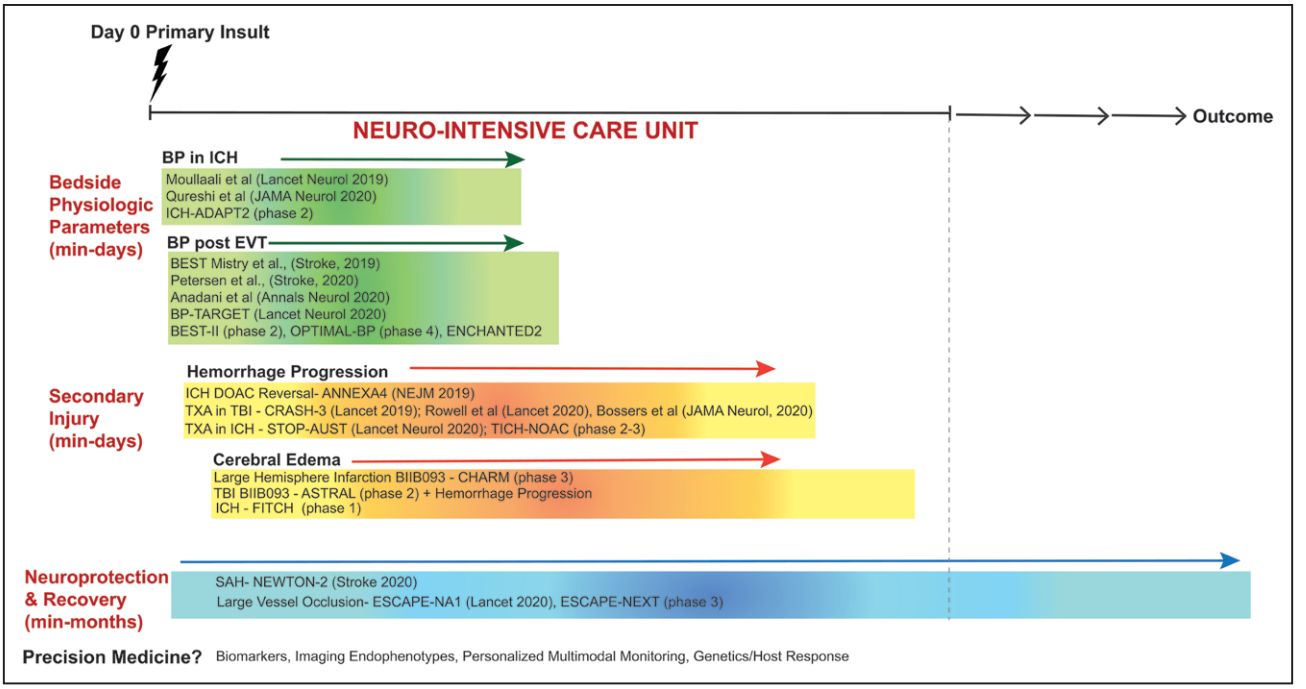

Figure. Key neurocritical care updates in cerebrovascular disease categorized by time from injury including bedside physiological parameters (blood pressure [BP]), secondary injury (hemorrhage progression and cerebral edema), and neuroprotection.
EVT indicates endovascular therapy; and ICH, intracerebral hemorrhage.

appear asymptomatic, recent evidence suggests that conventionally defined mild hemorrhagic transformation contributes to disability.[3]

The 2019 American Heart Association/American Stroke Association guideline updates recommend post-EVT BP ≤180/105 mm Hg (class IIb). However, higher SBP after recanalization is associated with unfavorable outcomes. Institutional practices vary: ≈24% adhere to the American Heart Association/American Stroke Association threshold.[4] In a multicenter prospective study (n=484), peak post-EVT SBPs >158 mm Hg increased the likelihood of unfavorable outcome (not significant in adjusted analyses).[5] A retrospective multicenter study (n=1019) compared SBP <140, <160, and <180 mm Hg after revascularization.[4] Both SBP <140 and <160 were preferable to <180 mm Hg: SBP <140 had higher odds of favorable functional outcome (odds ratio, 1.53 [95% CI, 1.07–2.19]) and lower odds of hemicraniectomy (odds ratio, 0.18 [CI, 0.16–0.21]). SBP <160 mm Hg decreased 90-day mortality odds (odds ratio, 0.41 [CI, 0.18–0.96]). The final infarct volumes were unknown. BP-recording methods and management varied. These data identified the need for RCTs.

BP-TARGET (Blood Pressure Target in Acute Stroke to Reduce Hemorrhage After Endovascular Therapy) randomized 324 patients to intensive (100–129) versus standard (130–185 mm Hg) management post-EVT.[3] Twenty-four- to 36-hour intracerebral hemorrhage (ICH) was no different, nor were secondary outcomes (functional independence and mortality). Achieved BPs were only modestly different between groups, 128±11 versus 138±17 mm Hg, limiting true comparisons of intensive versus liberal control. Another consideration involves the optimal SBP threshold post-EVT given the potential concerns of targeting SBP ≈120 s toward the nadir of the U-shaped curve associated with unfavorable outcome. Several trials like BEST-II ([Blood Pressure After Endovascular Stroke Therapy] phase 2, NCT04116112, ≤180 versus <160 versus <140 mm Hg), OPTIMAL-BP ([Outcome in Patients Treated With Intraarterial Thrombectomy - Optimal Blood Pressure Control] phase 4, NCT04205305, <180 versus <140), and ENCHANTED-2 ([Second Enhanced Control of Hypertension and Thrombectomy Stroke Study] NCT04140110, <120 versus 140–180 mm Hg) are ongoing. BP-TARGET highlights challenges of operationalizing treatment targets (even within trials) and the recurring theme that accounting for heterogeneity/patient-specific characteristics may be valuable in future RCTs. This is conceptually supported by a prospective study (n=90) where personalized, autoregulation-based BP targets post-EVT had a larger impact on outcome versus static thresholds (140 or 160 mm Hg).[6] Deviation from autoregulation-based targets increased secondary injury and unfavorable outcome.

SECONDARY INJURY

Hemorrhage Progression

Hemorrhage progression (HP) prognosticates unfavorable outcome in ICH and traumatic brain injury (TBI).

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Therapeutic anticoagulation increases this risk. Andexanet alfa, Food and Drug Administration approved in 2018, is the only selective agent for reversing life-threatening bleeding from factor-Xa inhibition. ANNEXA-4 ([Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors] n=352) demonstrated reduced anti-Xa activity with andexanet alfa. Sixty-four percent of these patients had ICH—effective hemostasis was achieved in 80% and anti-Xa activity reduction modestly predicted hemostatic efficacy (area under the curve=0.64).[7] Mortality was 14%, with thrombotic events in 10%. Andexanet alfa is ≈4× more expensive than 4-factor prothrombin complex concentrates. Retrospective work in ICH suggests similar hemostasis (≈81.8%) and possibly lower thrombosis (≈3.8%) with 4-factor prothrombin complex concentrates. No differences between 4-factor prothrombin complex concentrates and andexanet alfa in ICH have been demonstrated: a phase-4 study (NCT03661528) is recruiting.

Tranexamic acid is of interest given its inhibition of fibrinolysis. In TBI, the multicenter RCT CRASH-3 ([Clinical Randomisation of an Antifibrinolytic in Significant Head Injury]; n=12737) reported a small mortality benefit (absolute risk reduction, 1.7%) limited to mild-moderate TBI.[8] Eligibility versus enrollment data were not presented. Heterogeneity in local practices affects global generalizability (≈66% from Pakistan, Malaysia). A multicenter RCT of moderate-severe TBI (United States/Canada, n=1063) confirmed no improvement in hemorrhage progression or outcome.[9] A comparative effectiveness trial (n=1827) suggested increased mortality in severe TBI.[10] Results are similarly disappointing in ICH. In TICH-2 ([Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage]; n=2325), tranexamic acid within 8 hours minimally decreased ICH growth (1 mL, *P*=0.0432) without improving outcomes.[11] The multicenter phase-2 STOP-AUST (Spot Sign and Tranexamic Acid on Preventing ICH Growth - Australasia Trial) RCT (n=100) evaluated tranexamic acid within 4.5 hours using the spot sign to select patients—again, there were no differences in ICH growth, mortality, or complications.[12] The imaging biomarker possibly selected a more responsive population (8% difference in ICH growth versus 4% from TICH-2, nonsignificant). Earlier treatment may be beneficial (trend at ≤3 hours). Although these studies represent much needed progress informing patient selection and timing for future trials, the current impact of tranexamic acid in the neurointensive care unit seems limited.

Cerebral Edema

Cerebral edema causes acute neurological deterioration across a wide range of pathologies; insight into its biological underpinnings continues to exponentially increase. Although the classic taxonomy of cytotoxic/cellular versus vasogenic edema versus hemorrhage progression remains clinically informative, it is increasingly recognized that these processes represent a spectrum of edema evolution that may be molecularly related. Several promising targets have emerged including SUR1 (sulfonylurea receptor 1)-TRPM4 (transient receptor potential melastatin-4), S1P (sphingosine-1-phosphate), AQP4 (aquaporin-4), AVP (arginine vasopressin), sodium-hydrogen exchanger, Na-K-Cl cotransporter, and MMP9 (matrix metalloproteinase-9). Antivascular endothelial growth factor agents have long demonstrated antiedema benefit in glioblastoma. SUR1-TRPM4, S1P, and AVP inhibitors are currently in clinical trials.

SUR1-TRPM4—a cation channel uniquely upregulated after injury in major cell types of the neurovascular unit—results in sodium influx and oncotic edema. It overlaps with other molecular contributors to edema (AQP4 and MMP9). Preclinical inhibition with glibenclamide reduces secondary injury in several models. Earlier clinical trials in large hemispheric infarction and TBI have demonstrated promising reduction in cerebral edema and hemorrhage progression. An intravenous formulation (BIIB093) is under investigation in large hemispheric infarction (phase 3, CHARM [Cirara in Large Hemispheric Infarction Analyzing Modified Rankin and Mortality], NCT02864953) and contusional TBI (phase 2, ASTRAL [Antagonizing SUR1-TRPM4 to Reduce the Progression of Intracerebral Hematoma and Edema Surrounding Lesions], NCT03954041). Precision medicine–based selection of high-risk patients (biomarkers, imaging, and genetics) may inform future trial design. S1P subtype expression on endothelial cells and adherens junctions regulates blood brain barrier permeability via the cytoskeleton and endothelial morphology. Small studies of inhibition (fingolimod) suggest perihematomal edema reduction with ongoing evaluation in ICH (phase 1, FITCH [Fingolimod as a Treatment of Cerebral Edema After Intracerebral Hemorrhage], NCT04088630).

NEUROPROTECTION

In subarachnoid hemorrhage, NEWTON-2 (Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage) revealed no improvement in 90-day outcome with 600 mg intraventricular EG-1962 (sustained-release nimodipine) versus oral nimodipine.[13] A nonsignificant trend toward favorable outcome was seen in severe/high-grade cases. EG-1962 reduced angiographic vasospasm versus oral nimodipine (50% versus 63%; *P*=0.025) and hypotension (7% versus 10%). Given the absence of safety concerns, EG-1962 may have a role in severe cases/those on vasopressor agents.

EVT may transform neuroprotection in large vessel occlusion by facilitating drug delivery to newly reperfused tissue. Although the multicenter ESCAPE-NA1 (Safety and Efficacy of Nerinetide [NA-1] in Subjects Undergoing Endovascular Thrombectomy for Stroke) RCT evaluating the neuroprotectant nerinetide after EVT was neutral, a prespecified post hoc analysis in alteplase-ineligible patients

demonstrated improved outcome with treatment.[14] Lower drug levels were observed in alteplase-treated patients. This is biologically plausible given preclinical data that plasmin, generated by alteplase, cleaves/inactivates nerinetide. ESCAPE-NEXT ([Efficacy and Safety of Nerinetide in Participants With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy Excluding Thrombolysis] phase 3, NCT04462536) is evaluating nerinetide in alteplase-ineligible large vessel occlusion patients undergoing EVT. Finally, novel forms of acellular therapies are being developed in preclinical models.[15] Neuroprotection thus remains our Everest, with recent valiant efforts falling short but imparting valuable lessons.

ARTICLE INFORMATION

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