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Recovery and Rehabilitation after Intracerebral Hemorrhage

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Abstract

About half of patients survive intracerebral hemorrhage (ICH), but most are left with significant disability. Rehabilitation after ICH is the mainstay of treatment to reduce impairment, improve independence in activities, and return patients to meaningful participation in the community. The authors discuss the neuroplastic mechanisms underlying recovery in ICH, preclinical and clinical interventional studies to augment recovery, and the rehabilitative and medical management of post-ICH patients.

Keywords

intracerebral hemorrhage; impairment; disability; plasticity; recovery; rehabilitation

Intracerebral hemorrhage (ICH) is a devastating subtype of stroke, with mortality up to 50% by 1 month.[1,2] Although early clinical investigations have traditionally focused on mortality and its reduction, more recent efforts have begun to attend to disability in survivors. In this review, we concentrate on what happens to survivors following ICH and potential avenues of therapy to improve disability. We discuss ICH in its most common presentation: the nontraumatic deep cerebral or lobar hemorrhage typically resulting from hypertension.[3] We do not address the particular management of ICH in cerebral amyloid angiopathy, particularly because there is scant work specifically addressing recovery and rehabilitation in this population.[4]

Acute Pathophysiology of Stroke Subtypes

In rehabilitation, there is an inclination to consider ischemic and hemorrhagic stroke as variations on a theme, differing only in etiological insult and acute management. However, each entity has a unique subsequent pathophysiology (see review in[5]), and their neural recovery milieus and clinical recovery courses are also likely to differ.

In the hours to days following the energy failure and metabolic stress of ischemic stroke, excitotoxicity, oxidative insult, and inflammation lead to secondary cellular necrosis and apoptosis in peri-infarct tissue.[6,7] For several weeks after infarction, there is a robust uptick in cellular mechanisms mediating neuroplasticity. Increased neuronal excitability, axonal

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outgrowth, dendritic remodeling, and synaptogenesis counteract inflammation, axonal outgrowth inhibitors, and glial scar formation.[8,9] It is believed that this injury-induced plasticity is tuned by the activity-dependent plasticity brought about through training, resulting in the observed behavioral recovery.[10]

Compared with an equivalent-sized ischemic infarct, intraparenchymal blood results in greater cell death and inflammation.[11,12] In the first days following ICH, delayed metabolic changes, neuronal damage, and apoptosis in perihematomal tissue are believed to lead to more widespread consequences than the hematoma itself. Several pathophysiological processes are active: inflammatory damage mediated by cellular and noncellular components,[12,13] neurotoxicity related to hemoglobin-derived iron and free radicals,[5] and neuronal and glial apoptosis from thrombin.[14] In the face of a massive glutamate release post-ICH, genes important for neuronal signaling are rapidly downregulated, possibly as an endogenous neuroprotective mechanism.[15] The majority of preclinical research has focused on curtailing these early pathophysiological processes to improve outcome.[5]

The augmentation of neural reorganization may be another approach to improve outcome. It is generally believed that after an ICH, the CNS experiences some degree of injury-induced plasticity akin to that seen after an ischemic stroke. The processes that help or hinder reorganization in the first 3months following an ICH (i.e., the subacute period) are being actively characterized. One challenge in preclinical research is the use of different ICH-induction methods and different animal species, resulting in inconsistent histological and behavioral profiles.[16,17] In the most common model (collagenase-induced ICH in rodents), peri- and contrahematomal areas undergo neurogenesis,[18,19] dendritic branching,[20] dendritic reorganization,[21] and axonal spouting.[16] Although some of these histological changes have not yet been linked to behavioral change,[16,21] they are unlikely to be epiphenomena, and a more sensitive testing battery to precisely assay recovery may be required.[17] The drivers of neural reorganization and their relationship to behavioral recovery after ICH must still be clarified.

Natural History of Recovery

When evaluating human neurologic recovery, it is helpful to consider disability through the lens of the World Health Organization’s International Classification of Functioning, Disability and Health.[22] In this taxonomy, disability stems from dysfunction at three hierarchical levels: impairment of a body part or body function, limitation of activity performance (previously termed “functional limitation” or “disability”), and restriction of participation in a social context (previously termed “handicap”). These definitions structure our understanding of the impact of ICH on personal independence, and treatment approaches can be geared toward a particular level of dysfunction. Of note, instruments such as the Functional Independence Measure (FIM),[23] the modified Rankin Scale (mRS),[24] and the Barthel Index (BI)[25] capture activity limitation—the inability to perform an activity independently. These instruments do not identify the motor or cognitive impairments that underlie this limitation. Also, if activity independence is achieved, these instruments cannot distinguish if the underlying neurologic impairment has resolved or if the impairment has simply been circumvented with compensatory strategies (e.g., using the nonparetic arm to

successfully perform a task).While recovering independence in activities is most important for patient and family, characterizing the state of impairments is critical for mechanistic understanding, refinement of approaches, and therapeutic targeting. These considerations should be kept in mind when evaluating existing ICH outcomes research.

Given the pathophysiological differences between ischemic and hemorrhagic stroke, it is not surprising that clinical recovery courses also differ. The majority of human ICH research has focused on return to activity independence. By 6 to 32 months after an ICH, 50 to 64% of ICH survivors are independent in their activities of daily living (ADLs).[2,26] Although some have found comparable activity limitations in ischemic and hemorrhagic strokes,[27–29] others have found superior recovery of activity in ICH.[30–32] Similar findings have been observed when assessing the effect of comparable rehabilitation training in clinically matched hemorrhagic and ischemic stroke patients.[33] In this study, patients received the same type, amount, and duration of inpatient rehabilitation, administered by the same therapists. Relative to ischemic stroke patients, ICH patients had a greater rate of overall recovery, with less neurologic impairment and improved activity independence by time of discharge.[33] These finding are in keeping with a preclinical study matching ischemic or hemorrhagic lesions for size and location; rats with ICH have greater recovery of skilled walking ability than those with ischemic stroke.[34]

Less is known about the specific impairments associated with ICH. From cross-sectional observations, we know that ICH patients have many of the same sequelae as ischemic stroke patients, including aphasia,[35] neglect,[36] somatosensory loss,[37] cognitive dysfunction,[38,39] and depression.[40] Beyond this, there is a striking paucity of natural history documentation in ICH. The prevalence of the various ICH-related impairments and how they evolve over time is not well described. The impairments most problematic for independence in activities are not clear. Whether there exists a limited time window for maximal impairment recovery after ICH, when heightened neuroplasticity may best engage with our interventions, is not known. Without this important information, there is little guidance about where and when therapeutic efforts should be directed.

A recent step in the right direction was a longitudinal observational study of 11 patients over 6 months following ICH.[41] Investigators assessed the recovery of motor and sensory impairment and ambulation activity at four time points. Sensory impairment, lower limb motor impairment, and truncal motor impairment improved up to 3 months and plateaued thereafter; upper limb motor impairment and independence in ambulation continued to improve out to 6 months. Outcomes were not related to lesion size, age, or start time of rehabilitation.[41] Although this sample was too small to make population-level inferences, its conceptual approach was exactly right. To drive the rational application of therapies, the post-ICH landscape needs to be well characterized from behavioral, anatomical, and neurophysiological perspectives.

Neurorehabilitation for Intracerebral Hemorrhage

Preclinical Research

Although any intervention given after ICH could affect long-term function, we focus on those initiated beyond the first few days (i.e., the acute period). In preclinical ICH research, few studies have focused on rehabilitation approaches. A recent appraisal of ICH research in rodents found that the majority focused on neuroprotection or neurorestoration therapies; only 5% tested a rehabilitation therapy and only 10% measured behavior beyond 8 weeks post-ICH.[17] Preclinical neurorehabilitation research may provide useful behavioral and mechanistic insight into a therapeutic approach, though results are contextualized by model choice.[17] For pragmatic reasons, rehabilitation studies have primarily focused on motor recovery in rodents, usually using a collagenase model of ICH induction. We review these studies in consideration of their potential clinical translation.

Physical Training

Skilled reach training requires the animal to repeatedly reach and grasp edible pellets without compensatory truncal movements.[42] Skilled reaching activity improves with training,[21,43] and some animals also show improvements in skilled walking and spontaneous forelimb use.[44,45] Skilled reach training of the paretic forelimb increases bihemispheric brain-derived neurotrophic factor (BDNF),[44] bihemispheric dendritic reorganization,[21] and ipsilesional and bilateral sensorimotor astrocytic plasticity.[45] It also decreases mediators of apoptosis.[44]

Acrobatic training requires the animal to repeatedly traverse a route consisting of a grid, rope ladder, parallel bars, a rope, and vertical barriers.[46] Over the course of recovery, animals show gradual skilled walking gains, with accompanying increases in neuronal activation and synaptogenesis in the ipsilesional motor cortex and striatum.[46]

Aerobic training requires the animal to run on a treadmill or motorized wheel for a period of time. Daily training begun early (i.e., 4 days after ICH) improves motor impairments and walking ability.[47] Training started later (i.e., 2 weeks after ICH), even if more intense, does not improve reaching ability.[48] Treadmill exercise leads to migration of neuronal progenitor cells into the perilesional tissue,[49] increased neurogenesis, and increased BDNF signaling.[50] Behavioral improvements are accompanied by increased dendritic spine density and arborization in the contralesional striatum.[47]

Constraint-induced movement therapy requires restraint of the nonparetic forelimb to force use of the paretic forelimb.[51] Constraint-induced movement therapy and exercise training started within 1 week after ICH improves reaching and walking abilities,[52,53] whereas initiation 2.5 weeks after ICH results in less marked gains.[54] The behavioral benefit of an earlier start is associated with increased neuronal activation, expression of neurotrophins, and robust dendritic arborization in the ipsilesional, but not contralesional sensorimotor cortex.[54]

Environmental enrichment, using tunnels, ramps, toys, and a running wheel, provides the animal with an array of sensory stimuli and physical training opportunities.[55] When

environmental enrichment is paired with skilled reach training, animals often show improved skilled reaching and walking abilities,[43,56,57] but not always.[58] Behavioral changes are accompanied by increased dendritic length in bilateral striatum and ipsilesional sensorimotor cortex,[56] as well as reduced perihematomal neuronal degeneration.[57]

These preclinical studies collectively suggest that early and intensive behavioral training augments recovery after ICH, and that this training is accompanied by anatomical changes in the neural substrate. To most effectively translate these approaches to humans, the precise onset time, daily dose, daily frequency, and total duration of treatment to best promote recovery must still be established and ideally confirmed across models and species.

Brain Stimulation

An alternative approach for improving recovery is using brain stimulation to potentiate the effects of physical training. Vagal nerve stimulation (VNS) paired with training improves reaching ability in postischemic rats[59] and cortical map expansion in healthy training animals.[60] In post-ICH animals, VNS timed with behavioral training produces significantly higher gains in reaching ability.[61] Vagal nerve stimulation may increase neuromodulators participating in plasticity, like BDNF and prefrontal norepinephrine concentration.[62] Furthermore, acute administration in postischemic rats results in smaller infarct sizes without a clear influence on cerebral blood flow, suggesting a neuroprotective effect.[63,64]

Clinical Research

There are surprisingly few clinical rehabilitation studies specifically focusing on ICH patients. In larger randomized controlled neurorehabilitation trials, hemorrhagic stroke is often included alongside ischemic stroke, but small ICH samples usually preclude sufficiently powered subgroup analyses.[65,66] One study trialing gait training after stroke found a trend for larger ambulation gains in a lobar ICH subgroup, but specific responses to particular training interventions were not reported.[67] Three multicenter randomized controlled trials are currently assessing the effects of subacute fluoxetine on motor activity and depression after ischemic and hemorrhagic stroke.[68] Because these studies share a core protocol and are expected to collectively enroll 6,000 patients, the ICH sample may be sufficiently large to provide definitive answers about fluoxetine’s long-term efficacy and safety profile after ICH.

A recent randomized controlled trial in China investigated the effects of very early rehabilitation in 243 ICH patients.[69] With comparable clinical and neurologic baselines, groups began rehabilitation either within 48 hours or 1 week after ICH. Patients receiving very early rehabilitation had significantly shorter lengths of stay and lower mortality at 6months. In addition, early starters had significantly improved activity and participation relative to conventional rehabilitation.[69] Although these results seem to affirm that early rehabilitation promotes recovery, the study has some limitations. First, rehabilitation in China is delivered by family members. Beyond the limitation of generalization to Western practice, it is unclear if the content, quality, and duration of the training (including its continuation by the family at home) was equivalent across groups. Furthermore, because mortality predictors like lesion volume and location were not obtained, it is possible that

groups were imbalanced despite comparable clinical phenotypes. Finally, all behavioral outcomes were assessed by self-report of patients and families unblinded to their intervention group, raising the possibility of reporting bias. This study asks a very important question about the optimal timing of rehabilitation onset; future work using controlled interventions and objective outcomes may bring us closer to answers.

Noninvasive brain stimulation, such as transcranial direct current stimulation (tDCS), is being explored in ischemic stroke as a potential adjuvant to therapy (Clinical Trial #NCT00909714). Transcranial direct current stimulation induces a long-term potentiation-like effect and BDNF expression in vitro and improved motor skill learning in rodents and humans.[70,71] In a small double-blind study, 15 chronic ICH patients received either sham or real tDCS paired with occupational therapy for 5 days. The real stimulation group had improved grip strength immediately following the intervention, which did not persist to the 1-week follow-up and was not accompanied by an improved activity performance.[72] More robustly powered studies of noninvasive brain stimulation, ideally given in the subacute timeframe when this approach would be applied, are warranted.

Neurorehabilitation of ICH in Current Clinical Practice

In the absence of high-quality clinical data to guide specific practice, the rehabilitation of ICH patients is largely based on general principles learned from ischemic stroke recovery. To optimize plasticity and restoration of function after neural injury, neurorehabilitation should focus on functional but not compensatory training, should be started early and should be given at a high intensity and dose.[73] Even for ischemic stroke, however, specific parameters to guide day-to-day rehabilitation practices are lacking.

Rehabilitation services are provided in a variety of settings and at varied levels of intensity and duration. In inpatient rehabilitation (IRF), patients receive 3 hours of daily therapy 5 to 7 days per week, usually for less than 1 month. In skilled nursing facilities, patients receive 0.5 to 2 hours of daily therapy 5 to 6 days per week, for usually 1 to 2 months. In outpatient rehabilitation at home or at a facility, patients receive 0.5 to 1 hour of therapy 2 to 3 times per week, for usually 1 month.

Multiple considerations go into determining the best placement for the medically stable neurologic patient. For admission to an IRF, the patient must have impairments affecting mobility, independence in ADLs, and/or speech and swallowing. The patient must also be able to tolerate 3 hours of therapy daily and have 24-hour medical and nursing needs. Skilled nursing facility placement typically occurs when the patient is unable to tolerate this intensity of rehabilitation. Outpatient therapy is appropriate for patients with mild or few deficits, or it can follow a course of inpatient rehabilitation to extend functional training at home or in the community. Stroke patients receiving rehabilitation in an inpatient neurologic rehabilitation unit have significantly lower mortality and dependency than those in general medical rehabilitation units or nursing facilities.[74] To optimize morbidity and mortality outcomes, we attempt whenever possible to triage suitable ICH patients to inpatient rehabilitation units with expertise in neurologic rehabilitation.

Because ICH impairments typically span motor and cognitive domains, a comprehensive treatment plan is tailored to each patient. In ICH patients with neglect, ataxia, and lower extremity sensorimotor impairment, physical therapists train bed mobility, transfers, gait, balance, lower extremity range of motion and strength, and stair navigation. In ICH patients with upper extremity sensorimotor impairment, executive function impairment, apraxia, and ataxia, occupational therapists focus on optimizing ADL independence. Adaptive equipment (e.g., built-up utensils, walkers, tub benches, grab bars and rails) is used to improve safety and functionality at home. Speech and language pathologists address the dysphagia, dysarthria, aphasia, and cognitive impairments encountered in the ICH patient. The physician coordinates the rehabilitation team and medically optimizes the patient to enable participation in intensive therapy. The physician also actively manages general medical conditions such as depression, constipation, urinary incontinence, infection, malnutrition, and dehydration, in addition to ICH-related complications.

ICH-Related Complications

Several acute complications may extend into the weeks following ICH, overlapping the time when a patient may be on a rehabilitation service. These complications include seizures, recurrent bleeding, edema with mass effect, hydrocephalus, venous thromboembolic events, and hyper/hypotension. Intracranial pathology associated with ICH typically manifests as diminished arousal, positional headaches, cranial nerve palsies, or new/worsening focal deficits. Its rapid identification and initial workup is the role of the rehabilitation service. Sudden neurologic or medical decompensation typically warrants the patient's return to an acute hospital service where a higher level of clinical monitoring and/or intervention can be provided.

Seizures and Seizure Prophylaxis

Upwards of 90% of seizures occur within the first 3 days of ICH.[75,76] Seizure prophylaxis is associated with unchanged or worse outcomes and does not prevent long-term seizures.[77–80] The prophylactic use of antiepileptic drugs (AEDs) is thus discouraged by the American Heart Association (AHA), although seizure treatment with AEDs is warranted.[81] In a rehabilitation setting, AEDs should be tapered off in ICH patients without a history of seizure or electrographic abnormalities. If the patient does have a seizure, precipitants such as infection, electrolyte abnormalities, or rebleeding should be ruled out and an AED should be initiated.

Recurrent Bleeds and Anticoagulation

The risk of spontaneous rebleed is highest within the first year following the initial event, and occurs at a rate of 1 to 5% each year thereafter.[82] Risk factors for recurrent ICH include hypertension, older age, and lobar ICH.[83] During rehabilitation, patients will commonly experience fluctuations in blood pressure due to exertion, position changes, or straining, so surveillance for associated changes in neurologic status is obligatory.

Anticoagulant or antiplatelet medications may be necessary for prophylaxis against cardiac, cardiovascular, or hematologic thrombotic events. In these patients, AHA ICH management

guidelines recommend that warfarin for nonvalvular atrial fibrillation probably not be resumed after spontaneous lobar ICH, but may be considered after nonlobar ICH.[81] It is uncertain whether the use of dabigatran, rivaroxaban, or apixaban confers a lower risk of rebleed in these patients.[81] Although the optimal timing of resumption of anticoagulation is also uncertain, this should generally be deferred until 1 month after ICH unless high-risk sources for recurrent thromboembolism exist.[81] Aspirin monotherapy can probably be restarted within days after ICH. Resumption of these medications during rehabilitation is accompanied by close monitoring for neurologic change.

Perihematomal Edema and Hydrocephalus

Perihematomal edema is associated with mass effect and early neurologic decline, and is a predictor of poor functional outcome and mortality.[84–86] It typically reaches a maximum two weeks after ICH.[87] Hydrocephalus is associated with intraventricular extension (IVE) of the hemorrhage or cerebrospinal fluid (CSF) outflow obstruction from mass effect.[88] Intraventricular extension may cause hydrocephalus through inflammation and scarring of CSF outflow tracts.[89] For patients with very recent ICH with IVE, or with hemorrhage/edema in susceptible areas (e.g., cerebellum, brainstem), extension of close neurological monitoring into the rehabilitation period is warranted.

Venous Thromboembolism

Deep venous thromboses (DVTs) may limit participation in rehabilitation and can lead to potentially fatal pulmonary embolus (PE). In a meta-analysis of 1,000 ICH patients given enoxaparin or heparin thromboprophylaxis 1 to 6 days following ICH, the rate of PE is diminished without a significant reduction in mortality, DVT rate, or hematoma enlargement.[90] Per AHA ICH management guidelines, after documentation of hematoma stability, low-dose subcutaneous low-molecular weight heparin may be initiated 1 to 4 days after ICH for venous thromboembolism (VTE) prevention; observation alone for DVT or PE is not recommended.[81] In patients who develop VTE following ICH, systemic anticoagulation or an inferior vena cava filter are probably indicated, depending on the time from hemorrhage onset, hematoma stability, cause of hemorrhage, and overall patient condition.[81] If no contraindications exist, VTE prophylaxis is generally continued or initiated in rehabilitation in patients with diminished mobility.

Blood Pressure

In acute ICH, antihypertensive measures must often be initiated to achieve immediate blood pressure control.[81] The goal (blood pressure < 130/80 mm Hg) is maintained in the rehabilitation unit, although it is common for patients to gradually become hypotensive on their acute regimen. After ensuring a normal fluid balance, antihypertensive medications may be gradually decreased to enable participation in therapy while keeping within the recommended blood pressure parameters.[81]

Future Directions in the Neurorehabilitation of Intracerebral Hemorrhage

Disability reduction after ICH is an emerging area of interest and focus of treatment. Critically needed are natural history and interventional studies in ICH that detail recovery at

all levels of function. Optimal rehabilitation parameters—including content, onset time, dose, intensity, and duration—will need to be established for this specific group. Similarly, therapy adjuvants such as noninvasive brain stimulation and pharmacological agents will also need vetting in ICH patients. The current state of knowledge of ICH neurorehabilitation is limited. As research in this area becomes more rigorous and pointed, however, the potential impact of targeted therapies on recovery is enormous.

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