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CURRENT PERSPECTIVES

Advances in Therapeutic Approaches for Spontaneous Intracerebral Hemorrhage

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Abstract
Spontaneous intracerebral hemorrhage (ICH) results in high rates of morbidity and mortality, with intraventricular hemorrhage (IVH) being associated with even worse outcomes. Therapeutic interventions in acute ICH have continued to emerge with focus on arresting hemorrhage expansion, clot volume reduction of both intraventricular and parenchymal hematomas, and targeting perihematomal edema and inflammation. Large randomized controlled trials addressing the effectiveness of rapid blood pressure lowering, hemostatic therapy with platelet transfusion, and other clotting complexes and hematoma volume reduction using minimally invasive techniques have impacted clinical guidelines. We review the recent evolution in the management of acute spontaneous ICH, discussing which interventions have been shown to be safe and which may potentially improve outcomes.

Keywords Intracerebral hemorrhage · Intraventricular hemorrhage · Stroke · Outcomes · Fibrinolysis

Introduction

Spontaneous ICH represents 10–15% of all strokes worldwide but imposes significant morbidity and mortality [1]. It is estimated that 10–30 patients per 100,000 are affected annually with mortality rates as high as 50% in the first 30 days. Despite the widely recognized burden of this disease, there are disproportionately few proven interventions to improve clinical outcomes. However, over the past decade, emerging medical and surgical options show promising impact on functional outcomes. This review aims to detail existing and new medical and surgical advances within the field of ICH acute management and highlight future directions and ongoing studies.

Medical Management

Blood Pressure Control

Elevated blood pressure has been widely identified as a predisposing factor to hematoma expansion resulting in clinical deterioration [2]. However, uncertainty persists over blood pressure management in patients with ICH. Two large randomized clinical trials explored this aspect by investigating strict blood pressure control and correlation with death and functional outcomes. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) trial showed that intensive blood pressure management (systolic blood pressure [SBP] < 140 mmHg compared to SBP < 180 mmHg) does not affect hematoma volume, severe disability, or death but revealed a trend toward improved functional outcomes for the primary outcome measure [3]. Subsequently, the American Heart Association (AHA) guidelines were revised to state that acute lowering of SBP to < 140 mmHg is safe [4]. However, the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) trial, which compared a target SBP of 110 to 139 mmHg with a SBP range of 140 to 179 mmHg showed a similar rate of death and disability in the strict blood pressure control group when compared to standard management, with a higher rate of clinical deterioration, and possibly adverse renal events secondary to intensive blood pressure control [5]. Interestingly, a pooled analysis including data from the INTERACT2 and ATACH-II study showed that achieving a lower and less variable blood pressure goal is strongly associated with functional independence, lower mortality, less hematoma expansion, and less early neurologic deterioration. More specifically, it showed that every 10-mmHg reduction

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in SBP in the first 24 h to levels as low as 120–130 mmHg was associated with a 10% increase in the odds of better functional recovery, defined by modified Rankin Scale (mRS) at 90 days [6].

The discordant results between ATACH-II and INTERACT2 may be attributed to differences in methods by which blood pressure reduction was achieved in both trials. The ATACH-II trial achieved blood pressure reduction strictly with intravenous nicardipine, which might have resulted in a larger magnitude of early blood pressure reduction. INTERACT2 used variable blood pressure agents and required maintaining the target for 7 days or until hospital discharge, which may have resulted in a smoother trend in blood pressure reduction [7]. The pooled analysis of data from both trials by Moullali et al. supported this hypothesis of benefit from lowering SBP variability by showing that rapid and large reductions in SBP (≥ 60 mmHg) within the first hour of presentation were associated with potential harm [6]. SBP variability within 24 h of admission was further shown to be associated with worse function and in-hospital outcomes [8, 9].

Hemostasis

Antiplatelet use is controversial, with some, but not all, reports finding strong association with hematoma growth and increased mortality in patients with ICH [10, 11]. Several approaches have been explored to reverse the effect of antiplatelet agents. In a clinical trial of 190 ICH patients with prior antiplatelet use that randomized patients to standard care or standard care with platelet transfusion within 90 min of diagnostic brain imaging, platelet transfusion was not associated with clinical benefit at 90 days and raised the possibility of additional harm from platelet transfusion [12]. Hematoma growth was not different between groups, and serious adverse events were more frequent in the transfused versus standard care group (42% versus 29%, respectively). Guidelines thus recommend against platelet transfusion with the exception of patients planned for surgical intervention [13]. Desmopressin (DDAVP) has been investigated in two small studies that found that platelet function improved following DDAVP and that administration is safe, though no conclusions were made regarding hematoma expansion or clinical outcome due to the small sample size [14, 15]. Given the relatively safe profile of DDAVP and potential for benefit, guidelines recommend considering use in patients with prior antiplatelet use [13]. Desmopressin for reversal of antiplatelet agent effects in the setting of spontaneous ICH is currently being investigated with a phase II randomized clinical trial in the UK, Desmopressin for Reversal of Antiplatelet Drugs in Stroke due to Hemorrhage (DASH-NCT03696121).

Anticoagulation-related ICH represents a challenging dilemma. In patients with non-valvular atrial fibrillation on vitamin K antagonists, a dose-dependent risk of increased ICH incidence was reported with an INR > 4 [16]. Patients with oral anticoagulant-associated ICH are older, have larger ICH volumes, are more likely to have ICH and IVH expansion, and expand for longer periods of time [17]. Hence, reversal of the anticoagulant effect is likely important for improving clinical outcomes and preventing hematoma expansion, which can occur in as high as one out of three patients despite therapeutic INR levels. Thus, achieving an INR < 1.3 within the first 4 h of presentation was found to be necessary to reduce risk of hematoma expansion. Interestingly, SBP reduction to < 160 mmHg within the first 4 h was also associated with reduction in risk of hematoma expansion in patients receiving oral anticoagulation [17]. Combined approaches that include both BP lowering and reversal of anticoagulation could be important, as demonstrated in a recent health care delivery study [18].

Reversal agents for patients receiving VKA have been thoroughly investigated, resulting in clear guidelines. A randomized phase III trial compared fresh frozen plasma to 4-factor prothrombin concentrate (4-PCC) combined with vitamin K in ICH patients with an INR > 2 and acute surgical indication. Surgery was started earlier in patients who received 4-PCC, and patients in this group were able to achieve hemostasis more frequently [19]. Another randomized control trial was stopped prematurely since patients receiving 4-PCC had a significantly reduced rate of hematoma expansion with a strong trend toward reduced mortality at 90 days despite not reaching statistical significance [20]. As a result, guidelines dictate use of 4-PCC and intravenous vitamin K to lower INR < 1.3 as fast as possible in patients with ICH secondary to VKA use.

Patients with direct oral anticoagulant (DOAC)–associated ICH have a high rate of mortality and functional dependence with a significant incidence of hematoma expansion with intraventricular expansion [21]. Compared to VKAs, however, DOACs are associated with a lower risk of ICH, lower baseline hematoma volume, lower rate of hematoma expansion, and lower rates of in-hospital mortality [22–24]. Several antidotes have been shown to be efficacious in reversing DOAC effects. Studies specifically correlating that effect with hematoma expansion or clinical outcomes in patients with ICH are not yet available but are currently underway (NCT04062097, NCT03661528).

Idarucizumab (Praxbind) is a monoclonal antibody that binds to dabigatran with high affinity. The Reversal of Dabigatran Anticoagulant effect with idarucizumab (REVERSE AD) trial showed that idarucizumab is efficacious in reversing anticoagulant use [25]. The trial included mostly patients with gastrointestinal bleeding, but 32% of the cohort had ICH. Anticoagulant reversal was achieved in 100% of measured using the diluted thrombin time with 93.4% of patients achieving hemostasis prior to surgical intervention.

Median time to cessation of bleeding was 2.5 h and was maintained for another 24 h. The study concluded that idarucizumab can rapidly and safely reverse anticoagulant effect from dabigatran.

andexanet alfa is a recombinant modified human factor Xa decoy protein designed to reverse anticoagulant activity and approved by the FDA in May 2018 [26]. A prospective open-label study showed that factor Xa activity was restored in 93% of patients receiving apixaban and in 89% receiving rivaroxaban. Hemostasis was successfully achieved in 79% of cases [27]. Most recently, a single group cohort study (ANEXXA-4) showed concordant results in patients presenting with acute major bleeding with 89% of patients achieving good or excellent hemostatic activity within 12 h of administration [28]. The trial is still ongoing, as edoxaban reversal with andexanet alpha is being further evaluated. There have, however, been concerns regarding a higher rate of thrombotic events, which occurred in 10% of patients in addition to a rebound effect with a transient increase in D-dimer and prothrombin activity following administration [29].

The literature shows that PCC is efficacious in DOAC reversal in patients presenting with acute major hemorrhage with low risk of thromboembolism [30]. However, PCC showed no significant effect on the frequency of subsequent hematoma expansion or unfavorable outcome [31]. In one of the largest retrospective cohort studies of DOAC-associated ICH between 2011 and 2015, there were no significant differences in hematoma expansion, mortality, or 3-month functional outcomes between those treated with PCC compared to those without [31]. An ongoing trial aims to assess the efficacy of andexanet when compared to standard medical management in ICH within 12 h of symptom onset in patients receiving DOACs within 15 h (NCT03661528).

Tranexamic acid (TXA) is another antifibrinolytic agent that has garnered attention as a potential reversal agent for DOAC-associated ICH. A large international randomized trial, tranexamic acid for hyperacute primary IntraCerebral Hemorrhage (TICH-2), showed a reduction in early death but no significant effect on case fatality at 90 days or functional outcomes in a generalized ICH population receiving TXA compared to placebo within 8 h [32]. Further analysis showed a correlation with reduced hematoma expansion; the mean increase in hematoma volume from baseline to 24 h was 3.72 mL in the TXA group versus 4.90 mL in the placebo group. The study excluded patients receiving DOACs. A small randomized controlled trial (TICH-NOAC) is currently underway evaluating TXA in patients who received DOACs (NCT02866838). Another study is seeking to analyze whether treatment of hyperacute ICH with TXA within 2 h using a mobile stroke unit will yield positive effects on hematoma expansion and clinical outcomes (NCT03385928). Administration of recombinant factor VII (rVII) is not recommended, given robust data from the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial that it can increase the rate of thromboembolic events without significantly affecting long-term clinical outcomes [33].

Neuroinflammation

Accumulating evidence suggests that secondary brain injury through inflammation and microglia/macrophage activation plays a significant role in ICH. Activated macrophages express high levels of Toll-like receptor-4 (TLR-4), which have been correlated with neuroinflammation, chemokines, and cytokine release, including IL-1, IL6, and TNF-α [34]. Thus, modulation of the inflammatory response via inhibition of the TLR-4 signaling pathway or its end products can be a potential therapeutic target in ICH. To that end, preclinical studies have shown upregulation of IL-1Ra expression following ICH [35]. Clinical studies investigating the role of IL-1Ra inhibition are ongoing (BLOC-ICH, NCT03737344). TNF-α also plays an essential role in secondary brain injury in ICH. TNF-α antagonism was found to reduce PHE formation and improve neurologic outcomes in mouse and rat models [36, 37]. However, clinical studies evaluating TNF-α inhibition are lacking. Preliminary data from an ongoing trial (NCT04088630) showed that Fingolimod, a sphingosine-1 phosphate (S1P) receptor modulator, was effective in PHE reduction, improved neurologic outcome, and promoted recovery [38]. Another S1P receptor modulator, BAF312, is being investigated in a double-blinded clinical trial (NCT03338998).

Surgical Management

Craniotomy

Surgical management in patients with ICH includes craniotomy, craniectomy, and a range of minimally invasive surgery techniques. Clot removal has been hypothesized to improve ICH outcomes by relieving mass effect and cellular toxicity from residual blood products. However, a large randomized clinical trial evaluating early surgery vs. conservative management or deferred surgery, Surgical Trial in Traumatic IntraCerebral Hemorrhage (STICH I), showed a modest early mortality benefit but no clear long-term outcome benefits after clot removal in supratentorial ICH [39]. The results of the STICH I study suggested that some patients with superficial, easily accessible, and lobar hemorrhages may benefit from surgical intervention, which prompted a second randomized surgical trial, STICH II. STICH II investigated whether early surgery in lobar, easily accessible hemorrhages without IVH was beneficial, or not, in comparison to standard care. STICH II showed a small but clinically non-significant difference in survival in patients who underwent early surgical intervention

[40]. The two studies were faulted by a high crossover rate from the medical management to the surgical group in the setting of neurologic deterioration, likely diluting any possible clinical benefit from surgical intervention. The most recent systematic review and meta-analysis of 21 randomized clinical trials of surgical treatment in supratentorial ICH showed that the likelihood of good functional outcome was 40% higher in patients undergoing any surgical intervention when compared to medical treatment only [41]. Interestingly, the likelihood of good functional outcome was even higher (47%) in patients undergoing minimally invasive surgery (MIS) when compared to medical treatment only. Additionally, surgical interventions as a whole, and MIS specifically, lowered the risk of death when compared to medical treatment alone, (RR = 0.79, 95% CI = 0.66–0.94) and (RR = 0.68, 95% CI = 056–0.83), respectively. These interventions were more effective when surgery was performed sooner after symptom onset ($p = 0.04$). In contrast with a previous individual patient data meta-analysis [42], this meta-analysis did not find a modifying effect of age, Glasgow Coma Score (GCS) on admission, or ICH volume and suggests lower importance for restrictions based on age and GCS score in randomized controlled trials of surgery for ICH.

Decompressive Hemicraniectomy

The majority of earlier studies focused on a combined craniectomy and clot evacuation approach. The STICH trials raise the question of clot removal–related brain tissue injury [43]. Craniotomy was performed in 77% of surgical patients included in the STICH I trial, while 98% of patients in STICH II underwent craniotomy in the surgical arm [39, 40]. Decompressive hemicraniectomy (DC) is another strategy that alone can relieve elevated ICP and developing midline shift caused by mass effect and associated perihematomal edema (PHE) especially in ischemic stroke. Data regarding DC for ICH alone without clot retrieval are scarce and include a few case series. A case control study by Tung et al. with fifty-four patients who underwent DC found that the procedure improved survival without affecting functional outcomes. The survival benefit came at the cost of increased hospital stay and adverse events [44]. Other case series with fewer patients, but likely selection bias, did reveal an improvement in functional outcome when compared to medical management alone [45–47]. The largest uncontrolled case series included 73 patients who also underwent clot evacuation. The study concluded that DC is safe and feasible in ICH patients; 3-month functional outcomes were favorable in 29%, unfavorable in 44%, and 27% of patients expired [48]. Thus, the data on large craniectomy is sparse, and larger randomized clinical trials are needed to further evaluate the efficacy of DC in ICH patients. Accordingly, the SWITCH trial (decompressive hemicraniectomy in ICH patients) is a randomized controlled trial that was designed to determine whether decompressive surgery will improve outcomes compared to best medical treatment only in patients with supratentorial ICH (NCT02258919). Results from the SWITCH trial are still pending. Current ICH guidelines state that DC with or without hematoma evacuation might reduce mortality for patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management [4].

Minimally Invasive Surgery

Studies comparing MIS to conventional craniotomy have shown improved outcomes with a less-invasive approach, again raising the possibility that open craniotomy may damage brain tissue while removing blood. Earlier cases series found that patients with GCS > 6 and hematoma volume < 50 mL who received stereotactic surgery had better functional outcomes and shorter lengths of stay in the intensive care unit when compared to conventional craniotomy [49]. A meta-analysis in 2012 including 12 randomized clinical trials and 1955 patients showed that patients who underwent MIS had lower rates of death and physical dependence [50]. However, there were methodological issues such as combining craniotomy with conservative management in the comparison group [51]. A different meta-analysis included 15 studies and a total of 2155 patients who underwent MIS, either stereotactic thrombolysis or endoscopic procedures. The study concluded that both interventions decreased the incidence of moderate to severe functional impairment and death at long-term follow-up when compared to patients who underwent medical management alone or medical management and surgical craniotomy [52]. An ongoing large multicenter randomized clinical trial that plans to enroll 900 patients to undergo MIS is ongoing in China. The study aims to evaluate clinical efficacy of stereotactic thrombolysis or endoscopic surgery when compared to conventional craniotomy alone (MISICH, NCT02811614).

MIS has the appeal of relieving hematoma volume while minimizing disruption of healthy brain tissue when compared to conventional surgical methods. Therefore, there is increasing enthusiasm in exploring which surgical intervention is most beneficial in ICH patients and which patients are most likely to benefit. Stereotactic aspiration and thrombolysis was first investigated on a small scale in a case series including 15 patients that showed that hematoma volume and perihematomal edema were significantly reduced in the first 8 days [53]. This intervention, which is performed through a cranial burr hole, was further explored in the larger trials, Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation (MISTIE II) and MISTIE III. The MISTIE II trial was an open-label phase II clinical trial that included 54 patients in the MIS plus

alteplase group and 42 in the standard medical management group. The study showed similar safety outcomes of mortality, brain infection, and symptomatic hemorrhage in both groups, indicating that MIS plus thrombolysis is a safe and feasible approach in patients with supratentorial ICH [54]. A signal of 1% improved mRS 0–3 outcomes at 180 days was noted in this phase II trial. Improvement was proportional to amount of blood removed. These findings were the basis to launch MISTIE III to further evaluate clinical benefit from hematoma reduction. Two hundred forty-nine patients with ICH volume of > 30 mL were randomized to MIS plus thrombolysis and were compared to 250 patients who received standard medical treatment. Stability within 6 h of presentation was required prior to randomization, after which surgical patients underwent image-guided aspiration of the hematoma. A catheter was then inserted in the remaining hematoma followed by serial alteplase injections of 1 mg every 8 h up to 9 doses unless an adverse event arose. Surgical procedural success was defined as end of treatment (EOT) clot volume ≤ 15 mL. The mean hematoma reduction was 69%. The study concluded that good functional outcome (mRS 0–3) at 365 days was not significantly different between groups. Notably, only 58% of the patients in the surgical arm achieved the pre-specified EOT surgical procedural goal of ≤ 15 mL residual ICH volume. Further exploratory analysis showed that among the 146 surgical patients who reached an EOT volume ≤ 15 mL, 53.1% achieved a mRS 0–3 at 1 year compared to 32.7% of the patients with EOT clot volume > 15 mL ($p = 0.03$) (Fig. 1) [55].

A follow-up study evaluating thresholds of ICH removal in MISTIE III patients provided further insights into the necessary hematoma volume reduction to achieve improvement in outcomes. The data confirmed that clot volume reduction to ≤ 15 mL correlated with an improved functional outcome (mRS 0–3). The factors that predicted failure to achieve EOT clot volume ≤ 15 mL were found to be history of hypertension, higher initial ICH volume, greater number of alteplase doses administered, irregular-shaped hematoma, and importantly surgical center protocol deviations and catheter manipulation problems. Clot volume reduction beyond the 15 mL mark (or > 70% of clot volume) increased the chances of improved functional outcome by 10% for each additional milliliter removed ($p = 0.002$) (Fig. 2). A similar clot removal analysis showed improved survival outcomes at 1 year in patients with EOT clot volume < 30 mL [56].

Alternative, minimally invasive procedures that involve increased manipulation of brain tissues but are performed with a small craniotomy bone flap are now under investigation in clinical trials with evidence of excellent hematoma volume removal. Case series have shown that hematoma aspiration via BrainPath resulted in 90–95% reduction in hematoma volume with 52% of patients achieving an mRS ≤ 2 [57, 58]. Subsequently, Early Minimally Invasive surgery for removal of intracerebral hemorrhage (ENRICH) was designed to evaluate early surgical intervention (within 24 h) for ICH patients using the BrainPath Approach (i.e., MIPS). The trial is underway (NCT02880878). Time to treatment remains a controversial issue. Individual patient data demonstrate a significant impact of early surgery on outcomes in either trials of craniotomy or MIS, but are only able to state that trials of surgery with a time to evacuation up to 72 h have demonstrated efficacy over conventional therapy, though with early evacuations possibly driving the results [52]. New studies such as the DIST (Dutch Intracerebral hemorrhage Surgery Trial) aim to enroll patients in the acute and hyperacute period to evaluate effect. The pilot study will enroll 40 patients under the MIS arm within 8 h of presentation (NCT03608423). Currently, no trial data compares different devices for MIS in ICH. Such data may come from the INVEST study (Minimally Invasive Endoscopic Surgery with Apollo in Patients with Brain Hemorrhage), which aims to evaluate clot evacuation with the Apollo system versus the Artemis device in conjunction with penumbra aspiration (NCT02654015). MIND (Artemis in the Removal of Intracerebral Hemorrhage) is an ongoing trial that aims to evaluate the efficacy of clot removal using the Artemis evacuation device (NCT03342664).

MISTIE and perhaps other MIS techniques are mechanistically plausible surgical interventions. To date, large multisite trial evidence from MIS interventions that remove clot does not clearly delineate any functional outcome benefit from MIS procedures in ICH patients. Currently, guidelines for surgical evacuation of ICH suggest that clot removal in supratentorial ICH is not clearly established to improve outcomes, but can be considered a lifesaving measure for patients in a coma with midline shift or with refractory elevated ICP [4]. Moreover, based on the STICH trial data, a policy of early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate [4]. The AHA guidelines do not currently provide recommendation for selecting candidates for surgery, though the European ICH guidelines suggest that early surgery may be of value for patients with a GCS score of 9–12 [59]. The benefit behind MIS (endoscopic or stereotactic thrombolysis) is uncertain (class IIb, level of evidence B) [4]. However, based on available data, patients with supratentorial ICH who achieve EOT clot volume < 15 mL using clot fibrinolysis, may derive the most benefit.

Hematoma Evacuation and Cerebellar Hemorrhage

Surgical hematoma evacuation for cerebellar ICH has been the preferred method of treatment despite absence of randomized clinical trials. Surgical evacuation is especially considered in patients with large ICH volumes and IVH extension to avoid brainstem compression and ensuing complications. The 2015 AHA guidelines recommend surgical evacuation for patients with cerebellar ICH with

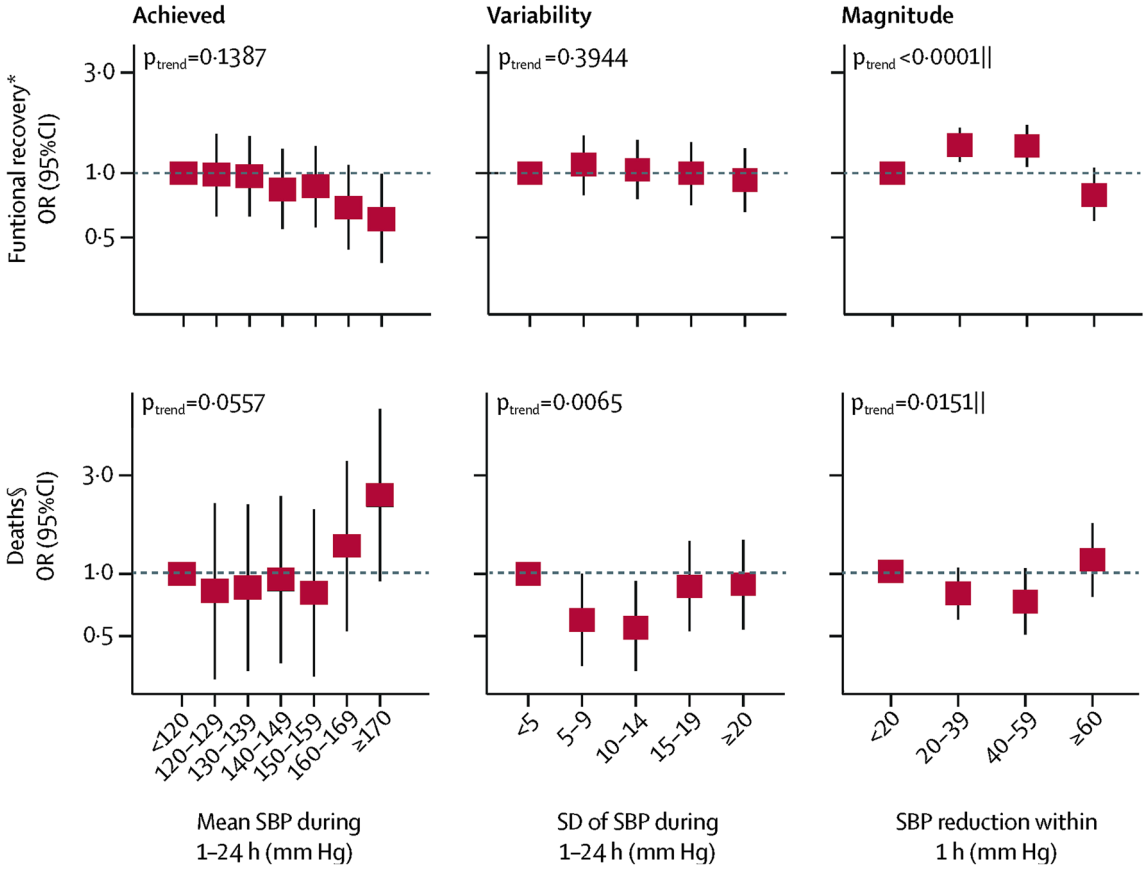

Fig. 1 Associations of categorized systolic blood pressure summary measures and clinical outcomes from the pooled INTERACT2 and the ATACH-II trials. These assessments of the systolic blood pressure (SBP) summary measures (mean achieved and standard deviation (variability) over first 24 h, and magnitude of change in SBP over first hour after treatment initiation) as categories show that generally lower categories of achieved SBP (left) seemed to be associated with better outcomes, down to 120–130 mmHg, although not significant in the categorical analysis (top), that lower variability (middle) was associated with weak evidence for associations with adverse outcomes, significant for death (bottom), and that U-shaped associations were apparent for increasing magnitude of decrease in SBP over the first 24 h (right). Reprinted from Moullaali et al. [6], Blood pressure control and clinical outcomes in acute intracerebral hemorrhage: a preplanned pooled analysis of individual participant data, Lancet Neurol. 2019;18:857–864 by permission of Elsevier

neurologic deterioration, and who have brainstem compression and/or have hydrocephalus (class III, *Level of Evidence C*) [4]. Recently, an individual participant data meta-analysis of four observational ICH studies incorporating 578 patients with cerebellar ICH propensity score-matched 152 patients with surgical hematoma evacuation versus 152 patients with conservative treatment [60]. The study showed no association between surgical evacuation and the primary outcome of improved functional outcome at 3 months, when compared to the medical management group. Survival was found to be higher at 3 and 12 months in the surgical treatment arm versus the medical management arm. Further, exploratory sub-analysis showed significant association between improved survival and surgical evacuation in patients with cerebellar ICH volume of 15 mL or greater. Further randomized clinical trials limited to patients with large cerebellar hematomas would be required to establish efficacy of surgical evacuation but may be precluded by ethical considerations.

Hematoma Expansion and Perihematomal Edema

Neurological deterioration in patients with ICH is attributed to several modifiable factors including acute hematoma growth, intraventricular expansion, and perihematomal edema [12]. Hematoma growth is an independent predictor of both mortality and functional outcomes [61]. Thus, identifying factors resulting in ICH growth can further guide patient management and design of randomized clinical trials targeting clinical benefit. A recent systematic review revealed that longer time from symptom onset to imaging, larger baseline volume of ICH, and use of antiplatelet and anticoagulant agents increased the probability of later ICH growth [62]. In patients not taking anticoagulants, the likelihood of hematoma growth decreased in time with the steepest decline being the first 0.5 h to 3 h following symptom onset [62]. Nevertheless, several trials investigating therapies to reduce hematoma expansion have all failed to reject the null hypothesis. The platelet transfusion versus standard care after acute stroke due to spontaneous

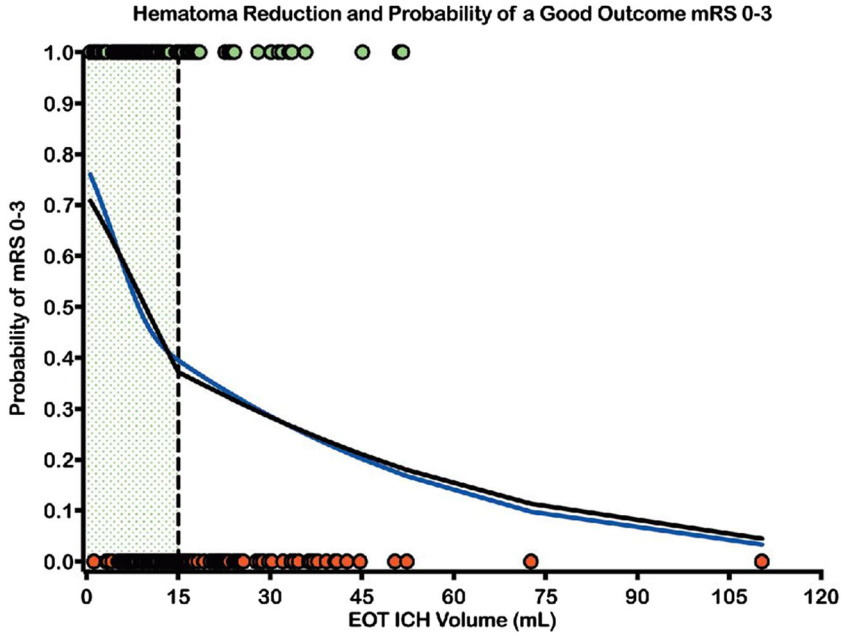

Fig. 2 Hematoma reduction and probability of a good outcome from the MISTIE III trial. Cubic spline regression analyses (blue line) and linear spline regression analyses (black line) showing the relationship of hematoma reduction (EOT ICH Volume) to the probability of having a good outcome, mRS 0 to 3, at 1 year. Outcome is dichotomized as 1 or 0 (green dots at 1 = mRS 0 to 3, red dots at 0 = mRS 4 to 6). Further reduction beyond the 15 mL threshold (OR 0.09, $P = 0.002$) increased the chance of having a good outcome by 10% for each additional milliliter of hematoma removed (green shading showing statistically significant area of curve). Volume reductions to > 15 mL threshold did not significantly impact the likelihood of achieving a good outcome. Reprinted from Awad et al. [56], Surgical performance determines functional outcome benefit in the Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation (MISTIE) procedure, Neurosurgery 2019;84:1157–1168, by permission of the Congress of Neurological Surgeons

cerebral hemorrhage associated with antiplatelet therapy (PATCH) trial showed that platelet administration did not reduce hematoma growth, and in fact was associated with increased odds of death and dependence in 3 months [12]. Similarly, the TICH-2 trial showed that though administration of tranexamic acid reduced hematoma growth at day 2 compared to placebo, there was no clear benefit in functional outcome at 90 days following event [32]. More recently, the Intracerebral Hemorrhage Deferoxamine trial (iDEF) enrolled a total of 294 patients with 144 patients assigned to intravenous deferoxamine as an iron chelator, which has anti-inflammatory/anti-edema properties in animal models [61]. The study results showed that though deferoxamine was safe, no benefit in neurologic outcome at 3 months was noted in the treatment group. A greater benefit at 90 days was demonstrated in a secondary analysis.

The association of perihematomal edema (PHE) with outcomes in ICH is controversial but a potentially important factor in secondary brain injury. PHE, especially within the first 72 h, is associated with more midline shift, herniation, and 6-month mortality [62]. A pooled analysis of participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT1 and INTERACT2) studies showed that PHE increases in size significantly within the first 24 h and has a strong association with worse functional outcomes [63]. However, other studies have shown conflicting results. A single-center prospective study including 133 patients showed that PHE volume only affected discharge outcomes in patients with baseline ICH volume ≤ 30 mL [64]. Additionally, data from the INTERACT1 trial alone showed that PHE growth was not significantly associated with death and functional outcome in 90 days [65].

Studies exploring medical management of PHE have been limited by multiple confounding factors including hematoma growth, timing of PHE measurement, and PHE calculation methods. Intensive blood pressure control was not observed to affect 24-h PHE growth in the ATACH II trial. Hyperosmolar therapy has been conventionally used to manage PHE, mainly using mannitol and hypertonic saline therapy. While the short-term effects of hyperosmolar therapy are well established, there have not been clear correlations with 90-day functional outcomes [66]. PHE is thought to arise via secondary brain injury mechanisms due to neuroinflammation. Accordingly, studies investigating the influence of sulfonylureas by inhibiting the sulfonylurea receptor 1 (*Sur1*)-transient receptor potential melastatin 4 (TRPM4) channel and matrix metallopeptidase 9 (MMP-9) have showed promising results. Sulfonylureas were found to have an anti-inflammatory effect that was associated with lower admission ICH volume, reduced PHE, and reduced ICH/PHE ratio in a

retrospective case control study of 21 diabetic patients [67]. To that end, the GATE-ICH study is investigating the role of glibenclamide in treating PHE in ICH (GATE-ICH, NCT03741530).

PHE refractory to medical management and resulting in clinical deterioration can be treated with decompressive hemicraniectomy, as previously discussed; however, the evidence is less robust than it is for edema associated with ischemic strokes [45]. More recently, data extrapolated from the MISTIE II trial showed that percent of clot minimally evacuated positively correlates with PHE reduction [68].

To summarize, no clear guidelines currently exist to address management of PHE. Hyperosmolar therapy and mannitol are the most used treatment modalities. However, studies targeting the neuroinflammatory cascade resulting in PHE are ongoing; additionally, DC can be a lifesaving measure in patients with rapidly developing PHE in ICH.

Intraventricular Hemorrhage

Intraventricular hemorrhage (IVH) is an independent risk factor of poor functional outcome in ICH patients [69]. There are four mechanisms by which IVH can affect ICH patients: acute obstructive hydrocephalus, mass effect caused by the clot, toxic products resulting in local tissue ischemia, and chronic hydrocephalus. Through the above mechanisms, mortality can increase from 21% in ICH patients without IVH to 50% in patients with IVH [70]. External ventricular drainage (EVD) has been traditionally used to address the injurious effects of IVH; however, issues of slow flow of cerebrospinal fluid (CSF) and catheter obstruction urged further exploration of interventions to improve IVH outcomes. Guidelines currently state that ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness [4].

Earlier case series and retrospective studies showed that use of thrombolytics in addition to external ventricular drainage was associated with more efficacious clot removal and as a result, decreased morbidity and mortality with a similar rate of complications [71–73]. A systematic review including 316 patients showed that intraventricular administration of thrombolytics in addition to EVD insertion was associated with better mortality and functional outcomes when compared to EVD insertion alone [74]. CLEAR III (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) was the largest prospective randomized trial to date for severe spontaneous IVH [75]. CLEAR III compares the efficacy of EVD plus intraventricular thrombolysis to EVD plus intraventricular saline (placebo) in the control group. The study included 500 patients who developed obstructive IVH secondary to ICH (volume < 30 mL). The study was neutral on the primary outcome of mRS 0–3 at 180 days between patients treated with intraventricular alteplase vs. saline but showed that > 80% IVH clot removal was an important endpoint for improvement in functional outcomes. Unfortunately, a relatively small percentage of patients who received thrombolytics achieved > 80% clot removal (33% in treatment group vs 10% in standard group). Patients who received intraventricular thrombolytics (compared to saline) had significantly lower mortality at 180 days (18% in the treatment group vs 29% in the saline group, hazard ratio 0.60 [95% confidence interval, 0.41–0.86], $P = 0.006$) (Fig. 3) [75]. A common interpretation of this trial, however, was that reduction in mortality occurred at the expense of an increased number of survivors with moderately severe to severe disability (mRS 4 and 5: 17% (alteplase group) versus 9% (saline group); $P = 0.007$). No difference was observed, however, in the proportion of patients in a vegetative state (3% in both groups measured by the extended Glasgow Outcome Scale). Safety parameters revealed that hemorrhage rates were

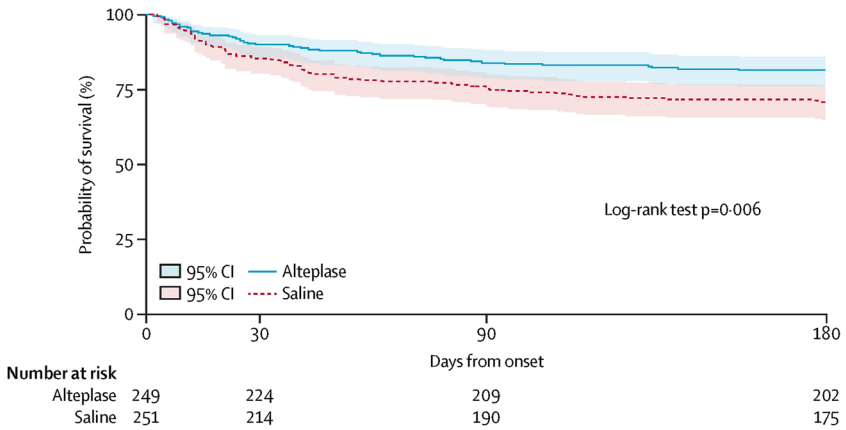

Fig. 3 Kaplan-Meier survival estimates from day of randomization to observed day of death from the CLEAR III trial. Estimated survival probabilities were higher throughout 180 days of follow-up with alteplase compared with saline ($p = 0{\cdot}006$). Shading shows 95% CI. Reprinted from Hanley et al. [75], The Lancet, 389, Thrombolytic removal of intraventricular hemorrhage in treatment of severe stroke: results of the randomized, multicenter, multi-region, placebo-controlled CLEAR III trial, 603–611, Copyright 2017, with permission from Elsevier

similar, but rates of bacterial ventriculitis and other adverse events were lower in patients who received thrombolytics [75].

Few prospective studies have explored endoscopic removal of intraventricular blood to decompress obstructive hydrocephalus. Investigators have found that in comparison to ventricular catheters, endoscopic surgery resulted in effective intraventricular clot removal with possible improvement in clinical neurologic outcomes; however, the studies included a small sample size, precluding robust conclusions [74, 76]. Safety of endoscopic removal has not been demonstrated. An important avenue of investigation has been the use of lumbar drainage (LD) following EVD insertion with or without thrombolytics with the objective of reducing permanent shunt dependence. A retrospective analysis showed that LD insertion in addition to an EVD in ICH patients with severe IVH decreased duration needed for CSF drainage and decreased the rate of permanent shunting [77]. A recent small randomized clinical trial investigated the rate of shunt dependence in patients treated with fibrinolysis via an EVD followed by LD insertion compared to patients treated with fibrinolysis via an EVD alone. The study was prematurely stopped after a preliminary analysis showed that LD plus fibrinolysis significantly reduced the rate of shunt dependence (to zero) with an absolute risk reduction of 24% [78]. Trial data is now consistent with the idea that removal of blood from the ventricles and CSF spaces must be vigorous and complete or perhaps nearly complete. Trials with protocols that lead to complete or near complete removal are needed. In conclusion, the AHA guidelines state that while clot evacuation using fibrinolysis is safe, its efficacy is uncertain (class IIb, level of evidence B) [4]. Based on the current findings, optimal benefit may be obtained from evacuating > 80% of initial clot volume. Large prospective studies are still needed to establish efficacy of endoscopic surgery and LD in IVH patients.

Conclusion

ICH remains a devastating disease with few interventions proven to influence outcomes. Medical management continues to revolve around blood pressure management, achieving hemostasis, and hyperosmolar therapy. With the advent of new technological advances, data from minimally invasive interventions addressing ICH and associated IVH appear to be promising. Several ongoing trials are expected to shed more light on the utility and timing of such procedures. An effective primary treatment will most likely require combining of critically important medical practices with a minimally invasive surgical procedure. The ideal criteria for selecting candidates for surgery remain unclear.

Compliance with Ethical Standards

Disclosures Dr. Hanley reports grants from NIH and personal fees from BrainScope, Neurotrope, Op2Lysis, Portola Pharmaceuticals, and medico-legal, outside the submitted work. Dr. Ziai has received grant support from NIH and compensation as a consultant for CR Bard Inc. and Portola Pharmaceuticals. Dr. Al-Kawaz reports no disclosures.

Unlabeled Use of Products/Investigational Use Disclosure Drs Al-Kawaz, Hanley, and Ziai report the unlabeled/investigational use of alteplase for the treatment of intracerebral hemorrhage.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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