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Thrombolytic Evacuation of Intracerebral and Intraventricular Hemorrhage

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Abstract

Intracranial hemorrhage (ICH) accounts for 10–15% of all strokes, however it causes 30–50% of stroke related mortality, disability and cost. The prevalence increases with age with only 2 cases/100,000/year for age less than 40 years to almost 350 cases/100,000/year for age more than 80 years. Several trials of open surgical evacuation of ICH have failed to show clear benefit over medical management. But, some small trials of minimal invasive hematoma evacuation in combination with thrombolytics have shown encouraging results. Based on these findings larger clinical trials are being undertaken to optimize and define therapeutic benefit of minimally invasive surgery in combination with thrombolytic clearance of hematoma. In this article we will review some of the background of minimally invasive surgery and the use of thrombolytics in the setting of ICH and intraventricular hemorrhage (IVH) and will highlight the early findings of MISTIE and CLEAR trials for these two entities respectively.

Keywords

Intracranial hemorrhage; intracerebral hemorrhage; Intraventricular hemorrhage; Minimally invasive surgery; thrombolytics

Introduction, Epidemiology and Scope of the Problem

Intracerebral hemorrhage (ICH), due to rupture of blood vessel in the brain parenchyma, can be divided into two broad categories: primary ICH and secondary ICH. ICH in the setting of pre-existing lesions like vascular malformation, tumor or in the setting of trauma is defined as secondary ICH. Primary ICH, the most frequent type of ICH and main focus of this article, refers to ICH in the absence of any clear underlying structural lesion. It is thought to be related to arteriosclerosis related to chronic and untreated hypertension, and amyloid angiopathy, which affects the arteries in the aged (1). Although spontaneous ICH with or without intraventricular hemorrhage (IVH) extension accounts for only 10–15% of all strokes, this devastating disease is associated with 30-day mortality rates of 35–52% and half of those deaths occur in the first 2 days (Fig. 1) (2–8).

Over the past few decades the frequency of all strokes has decreased, however this decrease has primarily been driven by the decreasing frequency of ischemic strokes (9). In case of ICH there is conflicting trend with studies reporting a decrease, stable and increase in the

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frequency (10–16). This conflicting trend can be explained by, on the one hand decrease in the frequency of hypertension related ICH due to improved medical management and on the other hand an increase in number of intracerebral hemorrhages related to increased use of anticoagulation (16). A meta-analysis of all the studies since 1980s by van Asch et al concluded that incidence of ICH increases with age and has not decreased between 1980 and 2006 (17).

Rationale for Volume Reduction in ICH

The poor outcome with ICH and the extent of associated brain damage can be correlated with the volume of parenchymal hemorrhage, and intraventricular hemorrhage. The blood mass produces direct destruction and compression of surrounding brain tissue. The volume of the hemorrhage elevates the intracranial pressure (ICP), affecting both cerebral perfusion and venous drainage. These vascular alterations are even more pronounced in the area of bleeding because of the direct mechanical effects, resulting in ischemia and poor perfusion to the damaged cells that need it most. The release of vasoactive and toxic substances from extravasated blood in the vicinity of the hematoma and the activation of the ischemic cascade further compound the brain damage and contribute to the morbidity and mortality associated with ICH. Volume of ICH is consistently shown to be a powerful predictor of poor outcome regardless of clot location, patient age, and neurological condition (18–22). In a large population based study Broderick et al showed that volume of ICH, in combination with the initial Glasgow Coma Scale (GCS) score, is a powerful and easy-to-use predictor of 30-day mortality and morbidity in patients with spontaneous ICH. In their study patients with parenchymal hemorrhage volume of 60cc or more on their initial CT and GCS of 8 or less had a predicted 30-day mortality of 91% while patients with a volume of less than 30cc and GCS of 9 or more had a predicted 30-day mortality of 19% (23). Several investigators have demonstrated that the damage and changes caused by ICH is a dynamic process and serial imaging studies have revealed that clot volume often progresses following the initial event (24–26). A study by Brott et al shows that within an hour after the initial scan, hemorrhage volume increases by one-third in 25% of patients and in about 10% of all patients, some additional increase occurs over the next 20 hours (25). There is a hypodense region surrounding the hematoma on CT scans, believed to be caused by serum extravasation from the blood collection itself and in 41% of patients, this area increases in volume over time and may contribute to the neurologic deficits. The impact of ICH volume on outcome has persisted despite modern critical care and aggressive treatment paradigms (27).

Several strategies of management of hemorrhagic stroke have aimed at limiting the volume of ICH and IVH, including rapid reversal of coagulopathy, and potentially more aggressive control of hypertension. But the burden of hemorrhagic stroke will nevertheless still reflect the volume of eventual ICH, which remains large and morbid in a significant fraction of patients, despite these proactive strategies.

The rationale for evacuation of ICH is based on the fact that larger hematomas result in more profound and longer-lasting alterations in adjacent brain parenchyma, attributed in part to mass effect and focal edema and reduction of clot volume may indeed improve neurological recovery and clinical outcome by removing focal mass effect, improving perfusion of compromised brain parenchyma and preventing intracranial hypertension. It also may enhance the clearance of blood breakdown products and thus preventing secondary brain edema and other potential neurotoxicity. Animal studies have in fact demonstrated that edema is diminished with the early evacuation of intracerebral clot (28).

Surgical Approaches to ICH Evacuation

Optimal treatment of ICH remains a complex and controversial issue with wide range of practice patterns. The spectrum of ICH ranges from large space occupying lesions that require surgery for acute neurological deterioration to small hematomas that should be managed conservatively, with equipoise about the management of lesions between these two extremes. Anecdotal reports document frequent dramatic recovery after emergent ICH evacuation in younger patients with impending brain herniation and these cases are typically excluded from clinical trials in ICH surgery, as are cases where ICH is caused by a vascular anomaly or tumor.

However, the majority of ICH cases affect mostly older patients, who decline slowly with a stable hematoma, and more likely with larger ICH volume. These cases have been shown not to fare as well with surgical intervention. Several clinical trials published between 1961 and 2004 failed to show clear benefit of surgical intervention over best medical management (29–38). In late 1980s Auer et al published a controlled randomized study of endoscopic evacuation versus medical treatment in 100 patients with spontaneous ICH and showed that surgical patients with hematomas smaller than 50 cc made a significantly better functional recovery than did patients of the medically treated group, but had a comparable mortality rate. Conversely, patients with larger hematomas showed significantly lower mortality rates after operation but had no better functional recovery than the medically treated group. This effect from surgery was limited to patients in a preoperatively alert or somnolent state; stuporous or comatose patients had no better outcome after surgery (30). Approximately 10 years later in late 1990s Zuccarello et al reported results from a small randomized feasibility study of early surgical treatment versus current non-operative management and found a trend toward a lower 3-month morbidity with surgical intervention (34). A meta analysis of all twelve trials published prior to 2006 gave an odds ratio of 0.85 (CI 0.71, 1.02) in favor of surgical treatment when the unfavorable outcome was death, and an odds ratio of 0.86 (CI 0.72, 1.03) for the 11 trials with published data when the unfavorable outcome was severe disability or death (39).

The largest clinical trial for surgical treatment of ICH, STICH trial, failed to demonstrate superiority of surgical treatment of ICH over medical management, however subgroup analysis showed that in the subset of 223 patient with lobar hematoma and no IVH, with initial conservative treatment 37% achieved a favorable outcome using the prognosis based outcome methodology where as 49% of patients achieved a favorable outcome with early surgery ($p = 0.080$). Furthermore using prognosis based Rankin as the outcome variable a significant benefit was observed for surgical patients in this subgroup ($p = 0.013$) (38). Since STICH lacked sufficient power to address this subgroup finding, STICH II trial was designed which compares craniotomy versus best medical therapy for lobar ICH and has completed enrollment, but results of follow-up have not been presented to date (40).

Application of stereotactic surgery and minimally invasive therapies to cerebrovascular surgery has led investigators to utilize such techniques toward the goal of reducing hematoma volume in the treatment of ICH. Minimally invasive surgical techniques may substantially decrease hematoma volume while avoiding the morbidity of major craniotomy procedure, especially in elderly and debilitated patients. In the randomized controlled trial performed by Auer et al ultrasound-guided endoscopic clot evacuation resulted in significantly lower mortality rates and improved clinical outcomes than medical treatment alone (30). Early attempts aimed at simple clot aspiration as well as more ingenious means of mechanical evacuation have failed to accomplish satisfactory volume reduction of ICH (41, 42). This has led to the adjunct use of fibrinolytic agents as a means of enhancing clot lysis and catheter drainage. Experimental studies have shown that infusion of urokinase

promotes clot lysis and resorption without producing neurotoxicity, histopathological alterations, or recurrent bleeding (43, 44).

Since the first report by Doi et al in which direct instillation of urokinase was used after stereotactic aspiration to liquefy the hematoma (45), several reports have favorably reported usefulness of urokinase in ICH volume reduction (46–50).

Thrombolytic Evacuation of the ICH

With the resurgence of modern stereotactic and image guided neurosurgical techniques, several case series of thrombolysis and catheter aspiration of ICH were published in the 1980's and 1990's suggesting that minimally invasive interventions are feasible, likely quite safe, and may avoid major surgical morbidity and offer improved outcome for selected patients with ICH (47, 48, 51, 52). In 2000 Montes et al reported preliminary experience with 12 consecutive cases of ICH treated by stereotactic CT-guided aspiration and thrombolysis with urokinase or recombinant tissue plasminogen activator (rtPA) (46). In this pilot series authors demonstrated that CT-guided thrombolysis and aspiration appears safe and effective in the reduction of ICH volume and this experience helped motivate the subsequent Phase II MISTIE trial. The Minimally Invasive Surgery and Thrombolysis in Intracerebral Hemorrhage (MISTIE) trial explored an aggressive avenue of treating ICH by combining minimally invasive surgery and local delivery of rtPA. MISTIE II was a phase II trial conducted from 2006 through 2011 evaluating safety, efficacy and dose escalation of rtPA in combination with minimally invasive surgery. In this trial patients with ICH volume of ≥ 20 cc and stable for 6 hours were treated with either 0.3mg or 1mg of rtPA every 8 hours to either final volume of <10 cc or 72 hrs. Preliminary results of this trial were recently presented at the International Stroke Conference in New Orleans in February 2012 (<http://braininjuryoutcomes.com/studies/mistie/entry/mistie/international-strokeconference-2012-mistie-phase-2-results>). These demonstrated reliable safety and feasibility of ICH clot removal. The trial also showed that the amount of clot removal was directly related to the catheter placement and positioning. Poor catheter placement score was associated with higher residual clot volume and suboptimal clot resolution. Careful planning of surgical trajectory for catheter placement, deployed in the final tier of the trial, resulted in improved performance by all participating surgeons. A trend toward therapeutic advantage was also demonstrated, with greater proportion of treated cases in better outcome strata, especially among cases with greater hematoma evacuation. In essence MISTIE II validated the proof of concept, feasibility of ICH volume reduction and confirmed safety of the technique in comparison to randomized controls with third party adjudication. Based on these findings, a Phase III trial is being planned, with sufficient power to delineate the treatment effect, which was seen in MISTIE II.

Enhancing the confidence in the MISTIE approach, a recently completed trial from China reported better outcome with minimally invasive thrombolytic evacuation of ICH with urokinase thrombolysis, as compared to open craniotomy (53), but this study was limited by the absence of a cohort treated without any surgical intervention.

The Problem of Intraventricular Hemorrhage

IVH is a frequent complication of ICH, and is often associated with another type of hemorrhagic stroke, aneurysmal subarachnoid hemorrhage (SAH). IVH can range anywhere from mild layering of the blood in the horns of the lateral ventricle to complete casting of all the ventricles and presence of IVH in the setting of either ICH or SAH is independently associated with a worse outcome (54–59). Even though it has been postulated that rupture of ICH into the ventricles would be beneficial in order to lessen the mass effect from the large ICH on surrounding structures, but in reality the extension of ICH into the ventricles has

been consistently demonstrated as an independent predictor of poor outcome in patients with ICH (60–64). In the setting of supratentorial ICH and IVH, a strong predictor exist between ventricular blood volume and poor outcome, and patients with more than 20cc of interventricular blood in general had poor outcome (65). A prospective study to determine the prognostic significance and pathophysiologic implication of intraventricular extension of ICH showed that 30-day mortality was much higher in patients with IVH and there was a direct correlation noticed between IVH volume and poor outcome. This correlation persisted when controlling for the presence or absence of hydrocephalus and size of associated ICH, thus establishing IVH volume as an independent prognostic factor of poor outcome, independent of the volume of ICH (60). In the setting of STICH trial it was noted that 42% of patients included in STICH with assessable scans also had an associated IVH. The prognosis for patients with IVH with or without hydrocephalus is much worse than that for ICH alone and removing these patients from the analysis and focusing on superficial hematomas presented a more encouraging picture for surgery (40). Similarly in the setting of aneurysmal SAH, impact of IVH has been noted to be an independently poor prognostic factor (59, 66, 67).

Several recent studies have attempted to grade the extent of IVH in relation to patient outcome (60, 64, 65, 68). The “Graeb score” takes into account the extent of involvement of the respective ventricles and associated ventriculomegaly, and has been extensively validated in outcomes studies (54, 64, 69).

Acute obstructive hydrocephalus from IVH causes elevated ICP, can lead to significant morbidity and mortality and is often treated with placement of external ventricular drain (EVD). However, the placement of EVD does not eliminate the morbidity and mortality of IVH, which is most likely due to underlying damage from the associated stroke, and the toxic effects of ventricular blood on adjacent periventricular brain tissue, including hippocampus, diencephalon and brainstem. It is generally agreed that the presence of hydrocephalus and deteriorating neurologic condition are an indication for placing an EVD, however the precise thresholds for insertion of EVD after IVH have not been clarified (70). An analysis of IVH cohort in a large prospective randomized study of surgery for ICH (71), demonstrated that continuous drainage of CSF contributes to the normalization of ICP. Catheter occlusions occur frequently in the setting of large IVH volume, with casting and clotting on ventricular blood, and these can result in poor ICP control. Catheter occlusions also require repeated catheter removals and insertions, thus increasing the risks of hemorrhage and infection (72).

Thrombolytic Clearance of IVH

The placement of EVD does not immediately clear the IVH, as the catheter may be obstructed by blood, or effect slow clearance of recalcitrant intraventricular blood cast. Blood clot resolution in CSF follows first-order kinetics, and the injection of thrombolytic agents into the ventricular space could increase the rate of clot resolution (73). Thrombolytic therapy for IVH has evolved in response to the problems of catheter obstruction and slow IVH clearance, and has been shown to be safe and effective in animal studies (74–76), and in small clinical case series (77–81). A systematic review of published retrospective case series comparing the outcome of conservative treatment, EVD and EVD combined with fibrinolysis in the setting of severe IVH due to SAH or ICH showed that the fatality rate for conservative treatment was 78%, for extraventricular drainage 58% and for EVD with fibrinolytic agents 6%; and the poor outcome rate for conservative treatment was 90%, EVD 89% and EVD with fibrinolytic agents 34% (82). In the setting of SAH, a prospective observational study by Nieuwkamp et al showed that massive IVH occurs in 10% of patients

with SAH and approximately half of these patients may benefit from intraventricular fibrinolysis (83).

With very large IVH (>40cc) with casting and mass effect the use of bilateral simultaneous EVD catheters may increase clot resolution with or without adjunctive thrombolytic therapy (84). On the other hand Staykov et al. found no difference in clot resolution between the groups treated with one vs. two EVDs in the setting of severe IVH; however they did find a trend towards a longer EVD duration and higher infection rate in the bilateral EVD group (85). The Staykov study did not include a comparison with single catheter cases, controlling for IVH volume.

Based on these smaller case series and animal models the safety and feasibility of intraventricular thrombolysis was tested in Phase II clinical trial (73), which showed that intraventricular thrombolysis with urokinase speeds the resolution of intraventricular blood clots when compared with treatment with ventricular drainage alone. In 2011 results of CLEAR II trial was published where 48 patients were treated with 3 mg rtPA or placebo and showed that patients in the treatment arm achieved more rapid clearance of IVH and improved outcome when treated with rtPA (86). Dose optimization, safety profile, and estimates of outcome have motivated an ongoing Phase III trial for more definitive assessment of the potential benefits of thrombolysis.

Conclusions

Hemorrhagic stroke remains one of the deadliest and most disabling diseases with high cost burden to the society. The treatment of ICH and associated IVH remains controversial with wide range of practice patterns, a lack of standardized therapeutic approach, and persistent poor management outcomes. Therapeutic nihilism has been compounded by the failure of early clinical trials of surgical treatment in comparison to medical management. However emerging results of minimally invasive thrombolytic evacuation of ICH and IVH in MISTIE and CLEAR, respectively, have been encouraging. Ongoing clinical trials promise to change clinical practice by integrating these novel strategies in the therapeutic armamentarium.

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Figure 1.
Head CT demonstrating large left sided ICH with IVH. There is blood in both lateral ventricles, left more than right.