Commentary

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A combination of Deferoxamine mesylate and minimally invasive surgery with hematoma lysis for evacuation of intracerebral hemorrhage

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Abstract

Intracerebral hemorrhage is associated with significant morbidity and mortality. Some clinical trials demonstrated a trend towards benefit with surgical evacuation of intracerebral hemorrhage, without strong statistically significant results. Subsequent studies focused on minimally invasive techniques. Improved outcomes were more likely with surgical reduction of intracerebral hemorrhage volume to $\leq$15 mL. Deferoxamine is currently being evaluated as a therapeutic tool in intracerebral hemorrhage with promising results. There continues to be a lack of level I evidence supporting medical and surgical tools for intracerebral hemorrhage evacuation. Could a combination of minimally invasive surgery with hematoma lysis and Deferoxamine result in more effective hematoma evacuation?

Keywords

Deferoxamine, intracerebral hemorrhage, hematoma lysis, intracerebral hematoma evacuation

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Intracerebral hemorrhage (ICH) is associated with significant morbidity. Mortality at one month is reported to be as high as 40%.[1] Although some trials have demonstrated a trend towards benefit with surgical evacuation of ICH, there continues to be a lack of level I evidence supporting this practice.[2]

The STICH trial showed a trend towards benefit for patients undergoing surgical evacuation of ICH, primarily in patients with lobar hematomas $\leq$1 cm from the cortical surface. This paved the way for the STICH II trial that enrolled patients with superficial lobar ICHs and at least a Glasgow Coma Scale (GCS) score of 7.[3] There was no statistically significant difference in outcomes between the surgical group and the conservative treatment group (unfavorable outcome in 59% versus 62% at six months, respectively, $p = 0.367$). However, about 50% of patients had a GCS $\geq$14. Patients in the poor prognosis group were more likely to benefit from surgery as compared to patients in the good prognosis group (odds ratio 0.49, $p = 0.02$). In addition, 21% of patients within the conservative treatment group had surgery and these still counted towards the medical management group given the intent to treat analysis. Further studies have shown that patients with intermediate GCS (9–13) tend to benefit the most from ICH evacuation.[3]

There is a strong association between ICH volume and poor clinical outcome.[4] Since no significant benefit was reported with craniotomy for ICH, subsequent studies have focused on techniques such as endoscopic and minimally invasive treatment. A retrospective review by Xu et al. reported that endoscopic removal

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of ICH was shown to be more effective and lead to better clinical outcomes as compared to craniotomy.[5] Several small randomized trials showed that minimally invasive surgery with administration of urokinase reduced the hemorrhage volume and may have improved functional outcomes.[6] MISTIE II, a phase 2 trial that recruited 96 patients showed safety of this non-craniotomy approach and reported that the method may produce a meaningful functional benefit.[7] This provided the rationale for MISTIE III, a phase 3 trial that evaluated functional outcome at 365 days post minimally invasive surgery and altelplase.[8] The surgical goal was to reduce ICH volume to $\leq$15 cc. MISTIE III did not reach the postulated goal; based on modified intention to treat population analysis, good functional outcome in the MISTIE group was 45% versus 41% in the medical treatment group ($p = 0.33$). Survival was modestly improved with the MISTIE protocol (mortality 23% in standard medical care versus 15% in MISTIE group, $p = 0.033$). Improved outcomes were more likely with surgical reduction of ICH volume to $\leq$15 mL; however, 41% of patients did not meet this target. There was a 10.5% difference in favorable outcome when ICH volume $\leq$15 mL was achieved as compared to best medical management ($p = 0.03$). Improving clinical outcomes in patients with ICH seems to go hand in hand with ability to achieve ICH evacuation to $\leq$15 mL on a consistent basis.

The i-DEF phase 2 trial evaluated clinical outcomes after Deferoxamine mesylate (32 mg/kg per day infusion for three consecutive days within 24 h of hemorrhage onset versus placebo).[9] When comparing clinical outcomes at day 90 between Deferoxamine and placebo, 34.3% versus 32.9% achieved an Modified Rankin Score (mRS) 0–2, respectively. This difference was more substantial at 180 days and in favor of the Deferoxamine group (mRS 0–2 45.2% with Deferoxamine versus 35.6% with placebo) and side effects were minimal. Clinical outcome exceeded the prespecified futility threshold at 180 days which was not met at 90 days. The current study chose to show a Upper Confidence Bound of 12%; however, the Hemorrhagic Stroke Academia Industry recently recommended that an absolute difference of 3% to 10% (average 5%) is acceptable.[10] Patients in the i-DEF trial had small hemorrhages (median ICH volume of 12.1 mL) and a mean GCS score at screening of 14; however, the NIHSS was 13, thus defining a moderate degree of disability. Still there was an observed benefit at 180 days with Deferoxamine in this population with ICH volume mostly less than 15 mL and primarily good GCS scores. Given the difference in outcomes at 180 days, Deferoxamine which is easy to administer and affordable warrants further investigation.

The findings of STICH II highlighted the preference to initially observe patients with a good clinical presentation and identify a subgroup of patients who may benefit the most from surgery; those who get worse or with initial moderate GCS score.[3] ICH onset to Deferoxamine initiation did not reveal a statistically significant difference in clinical outcome, but with the administration of Deferoxamine within 12 h of onset, peri-hematomal edema increased at a slower rate.[9] Could Deferoxamine provide a complementary early treatment paradigm in ICH?

Despite lack of strong evidence behind evacuation tools for ICH, management of ICH seems to be improving with time. Per the MISTIE III trial, functional independence had increased in patients by four-fold from 30 days to 365 days and 80% were at home or in active rehab at 365 days.[8] The mortality rate was low and greater than 40% of all patients achieved good functional outcome. Thus, outcomes of those with large ICH may not be as dismal as previously thought and further advancements in care are warranted.

Could a combination of minimally invasive surgery with hematoma lysis and Deferoxamine result in more effective hematoma evacuation and reach a clot size of less than 15 mL more consistently? We propose a randomized controlled trial to test this hypothesis with the hope of improving outcomes in ICH patients.

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