Middle meningeal artery embolization for chronic subdural hematoma: an effective treatment with a bright future

Michael R Levitt, Joshua A Hirsch, Michael Chen

Neurointerventionalists are participating in a transformative moment in the field, from expanded thrombectomy indications, to the endovascular treatment of hydrocephalus, and endovascular brain-computer interfaces. Perhaps most consequential in recent years is the endovascular treatment of subacute or chronic subdural hematoma (cSDH) via middle meningeal artery embolization (MMAE). First reported in 2000 as salvage therapy in patients with high surgical comorbidities, this treatment has grown in popularity as its safety and efficacy have been studied.

cSDH carries a high morbidity, mortality, and healthcare resource burden. Existing medical and surgical treatments, while effective, are imperfect, with recurrence rates of up to 20% and reoperation rates of 12%. These high rates were considered acceptable given the limited alternatives; adjunct medical treatment is at best moderately helpful, and at worst, harmful. In this setting, MMAE for cSDH emerged as a promising alternative. Recent meta-analysis found reoperation rates falling to 4.6% in cSDH treated with surgery and adjunctive MMAE, and 6.8% in cSDH treated with MMAE alone. These results, while favorable, were based primarily on case series and retrospective data collection.

The results of three randomized, prospective trials of MMAE for the treatment of cSDH were simultaneously reported at the International Stroke Conference 2024 meeting. Embolization of the Middle Meningeal Artery With Onyx Liquid Embolic System in the Treatment of Subacute and Chronic Subdural Hematoma (EMBOLISE) is an investigator-initiated but industry-sponsored multicenter, prospective, randomized, interventional, controlled, open label, adaptive design clinical trial of MMAE for patients with symptomatic cSDH across 39 centers in the USA using Onyx (Medtronic Neurovascular, Irvine, CA). EMBOLISE targeted enrollment of up to 600 patients across two arms. Patients with mild cSDH (defined as midline shift <5 mm, hematoma thickness ≤15 mm, and minor symptoms such as headache) were randomized 1:1 to either observation or MMAE, and patients with moderate or severe cSDH (defined as motor deficits, severe symptoms, midline shift ≥5 mm or hematoma thickness >15 mm) were randomized 1:1 to either surgery alone or surgery with adjunctive MMAE within 72 hours. Patients with bilateral cSDH were excluded if surgery was required on both sides. The primary endpoint was the rate of cSDH recurrence or progression requiring surgical treatment within 90 days. Secondary endpoints included technical success of MMAE, as well as non-inferiority of the MMAE cohort compared to the control cohort in each study arm in blinded assessment of functional outcomes (based on modified Rankin Scale (mRS)), number of hospital admissions, and change in radiographic appearance of cSDH (volume, midline shift or thickness) at 90 days. Safety endpoints were assessed at 90 and 180 days.

The observational arm of the trial is still enrolling, but the results of the surgical arm of EMBOLISE found that the interventional group (MMAE as an adjunct to surgery) met the primary endpoint. The rate of cSDH recurrence or progression requiring repeat surgical drainage was significantly lower in the interventional group compared with the control group of surgery alone (4.1% vs 11.3%; relative risk 0.36, 95% confidence interval (95% CI) 0.11 to 0.80, P=0.0081). The number needed to treat with MMAE to prevent one additional case of recurrence requiring repeat cSDH drainage was 13.8. The secondary clinical endpoint was also met, as the incidence of neurological deterioration (based on mRS) in patients in the MMAE group was non-inferior to the control group (11.9% vs 9.8%; non-inferiority margin 12%, P=0.0022). The rate of serious complications in the MMAE procedure was 2%, and there were no significant differences between the groups in the rate of stroke or neurological death within 90 days.

A second trial of MMAE for cSDH, Managing Non-Acute Subdural Hematoma Using Liquid Materials: A Chinese Randomized Trial of Middle Meningeal Artery Treatment (MAGIC-MT), is an investigator-initiated but industry-sponsored multicenter prospective randomized clinical trial of 722 patients across 31 centers in China. Details of the study protocol have been previously published, but briefly, MAGIC-MT also included two arms (burr-hole drainage or conservative treatment) with patients

<table>
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randomized 1:1 to receive MMAE with Onyx. Again, bilateral cSDH patients were not included if symptoms were not attributable to a single side. In contrast to EMBOLISE, MAGIC-MT excluded patients in whom craniotomy was performed, as well as patients with a pre-treatment mRS ≥2, and MMAE had to be performed before burr hole drainage in the surgical group. Endpoints were similar to EMBOLISE, including a primary endpoint of the rate of symptomatic cSDH recurrence or progression requiring surgical treatment within 90 days, and similar secondary endpoints.

MAGIC-MT also met the primary endpoint. Patients who received MMAE (either as an adjunct to cSDH surgery, or in the case of mild disease as a stand-alone treatment) were significantly less likely than the control group (burr hole drainage or conservative treatment) to require repeat cSDH treatment (7.2% vs 12.2%; odds ratio (OR) = −4.92, 95% CI = −9.37 to 0.63, P = 0.02). There were significantly fewer serious adverse events within 90 days in the interventional group (6.7% vs 11.6%; OR 0.54, 95% CI 0.32 to 0.92, P = 0.02).

The Squid Trial for the Embolization of the MMA for the treatment of cSDH (STEM), an industry-supported multicenter prospective randomized clinical trial across 33 centers in the USA, France, and Spain, was the third trial to be reported. STEM enrolled 310 patients with symptomatic cSDH, randomized 1:1 to either standard management (burr hole drainage or observation, with or without MMAE) using Squid (Balt, Montmorency, France). Unlike EMBOLISE, patients were excluded if a craniotomy was performed, as were patients with pre-treatment mRS ≥2. The primary outcome measure of STEM was cSDH recurrence or progression requiring surgical treatment at 180 days, with other secondary endpoints also at 180 days.

STEM, like EMBOLISE and MAGIC-MT, found that standard management with MMAE was superior to standard management alone in preventing cSDH recurrence or progression (15.2% vs 39.2%; OR 3.60, 95% CI 1.91 to 6.78, P = 0.0001). Interestingly, the positive effect of MMAE was primarily driven by patients who underwent stand-alone MMAE compared with observation (19.1% vs 59.2%; OR 6.70, 95% CI 2.43 to 19.10, P = 0.0001), while the effect in patients with MMAE as a surgical adjunct was numerically but not statistically superior to surgery alone (12.3% vs 25.4%; OR 2.40, 95% CI 0.97 to 6.03, P = 0.058). There was no difference in safety outcomes between the groups.

Taken together, these three trials indicate that MMAE for cSDH is safe and effective in preventing cSDH recurrence or progression, particularly as an adjunct to surgical treatment, and should be considered routinely in the course of clinical care. This represents a major shift in the management of cSDH, and legitimizes its categorization as a cerebrovascular disease. Corroborating trials are forthcoming and may provide additional strength to these results, particularly in the role of MMAE as a stand-alone cSDH treatment, as well as in patients with bilateral cSDH and in the setting of comorbid conditions such as patients requiring anti-coagulation. Ongoing randomized multicenter trials will assess these and other issues, as well as evaluating the efficacy of other embolization agents (table 1). There is still much to learn.

The incidence of cSDH is expected to rise as the population ages. Thus, the results of these and other studies will become even more important as the burden of disease increases. While we await further results, the results of these randomized trials provide, for the first time, level 2 evidence of clinical benefit for MMAE with liquid embolics in cSDH. Neurointerventionalists should play a key role in the treatment of patients with cSDH.

**Commentary**

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