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LETTER TO THE EDITOR

Middle meningeal artery embolization: an emerging treatment for non-acute subdural hematomas

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Dear Editor,

Subdural hematoma (SDH) is a type of intracranial hemorrhage that is characterized by the accumulation of blood in the subdural space.[1] Although numerous conditions, such as coagulopathy, neoplasms, vascular malformations, aneurysms, and alcohol and cocaine use can lead to SDH, acute SDH is more often caused by head trauma.[1] An acute SDH may resolve by reabsorption or, alternatively, it can progress to chronic SDH, generally by encapsulation and a complex process involving inflammation, angiogenesis, and fibrinolysis.[2, 3] The incidence of chronic SDH is reportedly increasing, probably due to population aging and increased use of antiplatelet and anticoagulant medication.[2]

The standard treatment for thick, compressive, or symptomatic SDH remains neurosurgical evacuation.[4] However, middle meningeal artery embolization (MMAE), a neurointerventional endovascular procedure that occludes the blood vessels contributing to the growth of chronic SDH,[1] has recently gained attention as a promising technique for managing this condition. In November 2024, three notable randomized controlled trials (RCTs)[5-7] that evaluated MMAE were published.

The EMBOLISE[5] trial was a multicenter, open-label, adaptive-design RCT conducted in the United States.[5] It included 400 patients with symptomatic, thick, or midline-shifting subacute or chronic SDH with an indication for surgery (burr-hole or craniotomy).[5] Patients were randomized to MMAE plus surgery (197 patients) or surgery alone (203 patients) groups, utilizing the Onyx liquid embolic system (Medtronic, study sponsor and collaborator) as the embolic agent.[5] A statistically significant 64% relative reduction in hematoma recurrence or progression requiring repeat surgery within 90 days was observed.[5] No significant inter-group difference was found in neurological deterioration at 90 days (measured using the modified Rankin Scale) in a non-inferiority analysis.[5] Mortality was slightly higher in the MMAE group (5.1% *versus* 3.0%), but was not considered to be related to the procedure or embolic agent.[5] No significant differences were observed in the incidence of stroke, although two patients in the MMAE group experienced procedure-related disabling strokes within the first month.[5] Importantly, the confidence intervals for additional efficacy endpoints and safety outcomes were not adjusted for multiplicity and should not be used for statistical inference.[5]

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The MAGIC-MT[6] was a multicenter, open-label RCT conducted in China that enrolled 727 patients with symptomatic non-acute SDH with mass effect who were previously independent in everyday activities.[6] Patients requiring craniotomy, emergency evacuation, or presenting with bilateral SDH with uncertain laterality of symptoms were excluded.[6] Patients were first categorized according to the need for burr-hole drainage, as judged by the treating neurosurgeon.[6] They were then randomized to MMAE (365 patients) or usual care (362 patients), which included burr-hole drainage, medical treatment, or both.[6] Onyx was again used as the embolic agent, although the study sponsors (including Medtronic) reportedly had no significant involvement in the trial's conduct.[6] The primary outcome, symptomatic SDH recurrence or progression of SDH within 90 days, showed no statistically significant difference between the two groups.[6] Exploratory subgroup analyses suggested possible benefits for patients not undergoing burr-hole drainage, those with a midline shift <10mm, or those who had never smoked; however, these results were not adjusted for multiplicity and cannot support causal inference.[6] Secondary outcomes included both clinical and imaging measures, but these were also not multiplicity-adjusted.[6] Interestingly, unlike the EMBOLISE[5] trial, a significant 42% relative reduction in the rate of serious adverse events (including death) within 90 days was observed in the MMAE group, although the 90-day mortality and rates of selected adverse events were unaffected.[6] MMAE-related complications included one case of facial nerve palsy and two allergic reactions to the contrast agent.[6] A notable limitation was the high proportion of patients who had previously undergone surgery, complicating the evaluation of the efficacy of MMAE in conservatively treated cases.[6]

The STEM[7] trial was an international, multicenter, open-label RCT that evaluated 310 patients with symptomatic chronic SDH >10mm on imaging.[7] Patients were previously submitted to standard surgical or non-surgical treatment, and those undergoing craniotomy or those with a previous modified Rankin scale score >1 were excluded.[7] Both unilateral and bilateral SDH were eligible, provided the inclusion and exclusion criteria were met.[7] Patients were randomized to MMAE plus standard therapy (surgical or non-surgical, 149 patients) or standard therapy alone (161 patients).[7] Surgical standard treatment included either burr-hole evacuation or subdural evacuating port system drainage.[7] Unlike the previous two trials,[5,6] the Squid liquid embolic agent (Balt USA, study sponsor and collaborator) was used in this trial.[7] The primary efficacy outcome, a composite of recurrent or residual SDH >10mm, reoperation, or major adverse events (*e.g.*, disabling stroke, myocardial infarction, or death by neurological causes) within 180 days, showed a statistically significant 64% reduction in the odds ratio.[7] The most frequent event in both groups was reoperation (20% combined).[7] No significant difference in the primary safety outcome (composite of disabling stroke or death within 30 days) was found between the two groups (both groups: 3%).[7] However, the 180-day mortality rate was slightly higher in the MMAE group (8% *versus* 5%), although the difference was not statistically significant.[7] Again, the widths of some confidence intervals were not adjusted for multiplicity, preventing its use in place of hypothesis testing.[7]

A meta-analysis[8] of these three RCTs[5-7] revealed mixed findings. Using a random-effects model, which was deemed preferable due to between-study heterogeneity, MMAE was found to significantly reduce reoperation rates at 90 days by 57% in surgical patients, and progression or surgical rescue in non-surgical patients by 64%.[8] However, there were no significant differences in the trial's pooled primary outcomes (mostly recurrence or progression) between the combined groups or functional outcomes.[8] Notably, a fixed-effects model showed a significant protective effect of 50% overall, 40% in surgical patients, and 64% in those managed non-surgically.[8]

Recently, a prospective single-center RCT conducted in Brazil from 2021 to 2024 evaluated the effectiveness of MMAE using Histoacryl as an adjuvant to surgical treatment of chronic SDH.[9] A total of 76 hematomas were randomized to receive either surgery alone or surgery followed by MMAE.[9] Recurrence occurred in 4.2% of the MMAE group and 12.5% in the control group, with no significant differences in mortality, length of stay, or complication rates.[9] Notably, embolization was performed using N-butyl-2-cyanoacrylate (Histoacryl) mixed with Lipiodol, which has demonstrated good distal penetration and safety.[9] Although the difference in recurrence rates was not statistically significant, this study supported MMAE with Histoacryl as a promising adjunctive approach for the management of chronic SDH, especially in resource-limited settings where alternative agents, such as Onyx or Squid, are cost-prohibitive.[9]

In summary, MMAE has emerged as a promising adjunct or potential alternative to conventional neurosurgical approaches for the management of non-acute SDH. As of November 2024, 21 trial protocols on this topic have been registered, and many of these

trials were ongoing and recruiting.[8] The publication of further RCTs will likely prompt updated meta-analyses, ideally incorporating advanced methods such as trial sequential analysis[10] to better clarify the true efficacy, safety, cost-effectiveness, and optimal embolic agent for this increasingly relevant intervention.[8]

DATA AVAILABILITY

The underlying content is contained within the manuscript.

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