PANEL DISCUSSION

Unmet Clinical Needs in Chronic Subdural Hematoma

Experts share their treatment approaches, common pitfalls to avoid, upcoming clinical trials, and predictions for the future of chronic SDH care.

With Fawaz Al-Mufti, MD; Adam S. Arthur, MD, MPH; Violiza Inoa, MD; and Jared Knopman, MD

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What are the keys to assessing patient candidacy for embolization in the setting of chronic subdural hematoma (SDH)?

Dr. Al-Mufti: I believe one of the most important factors to consider is the need to initiate anticoagulation or antiplatelet therapy when there is an urgent or even semiurgent concern that a chronic SDH will expand. In my experience as a clinician facing these difficult decisions, embolization of the membrane can theoretically reduce the risk of rebleeding.

Dr. Arthur: Currently, we do not have level 1 evidence to indicate this procedure in any patient group, but that may change in the next 12 to 18 months. In the meantime, based on the literature to date, it makes sense to consider this therapy in patients who

are symptomatic from chronic SDH and are at risk for recurrence or progression. Embolization can be considered as either a stand-alone therapy or in conjunction with surgical drainage, depending on the patient.

Dr. Inoa: In order to evaluate a patient with chronic SDH and their candidacy for treatment, one of the most important factors includes the patient's symptomatology; asymptomatic patients are treated conservatively, and embolization is generally reserved for patients with symptoms directly related to the SDH. Some of the symptoms include increasing or intractable headaches, cognitive decline, gait instability, seizures, focal neurologic deficits, mass effect, or midline shift. The symptoms and comorbidities also help determine if middle meningeal artery (MMA) embolization could be used as the sole versus an adjunctive mode of treatment. When hematoma evacuation is acutely indicated, embolization alone should not be offered, as the embolization should not interfere with the standard of care for these patients. Before clinical trials were available, MMA embolization alone was often considered for sizable chronic SDH with focal mass effect and mild neurologic symptoms, in poor surgical candidates, or as adjunctive treatment to surgery for patients with recurrent SDH or high risk for recurrence. In our current practice, patients who are candidates for embolization are routinely screened and randomized into a clinical trial, as we believe that randomized data will be useful to determine the best treatment strategy for this condition.

Dr. Knopman: I feel that nearly all patients with chronic and subacute SDHs are candidates for embolization, either as an adjunct to surgical drainage in cases with mass effect, as a primary treatment modality to prevent progression, or as a way to address radiographic recurrence or progression after initial treatment. The age of the SDH determines candidacy, as subacute and chronic SDHs have had the requisite time to develop membranes, which are the ultimate target for embolization. Patients on anticoagulation or with platelet/coagulation deficiencies are also excellent candidates for this procedure, as transradial access is safe in this coagulopathic patient population and few alternative options for treatment exist.

What are your considerations when deciding on optimal access—radial or femoral, as well as a unilateral or bilateral approach?

Dr. Inoa: Optimal access and support are essential to ease the navigation through distal and sometimes tortuous MMA branches. Transfemoral access is still the preferred route in our practice, unless there is an available vessel imaging study that favors a transradial approach. Given that this condition affects mostly older patients, there is a higher chance for vascular tortuosity and unfavorable anatomy for radial access, such as proximal carotid artery loops or a double subclavian innominate curve. As most patients don't have a vascular study for review prior to their procedure, we have opted to start with femoral access as there might be more catheter flexibility in case carotid access proves to be too challenging.

When there is bilateral SDH, our approach has been to treat the symptomatic side first, followed by the asymptomatic side. For patients with unilateral SDH, we treat the affected side only. We have seen patients with unilateral SDH that have a contralateral recurrence, which makes us wonder about prophylactic treatment indications of the unaffected side. At this point, there are no randomized data available to guide our practice, and the decision regarding unilateral versus bilateral treatment approaches is left to the discretion of the treating provider.

Dr. Al-Mufti: Whenever possible, I opt for a radial approach, but I like to tailor my access site depending on my patient—neither a radial-first nor femoral-first but rather a patient-first approach. I consider the patient's need and vascular anatomy to individualize my treatment approach. I reserve bilateral MMA embolization for patients with bilateral SDHs.

Dr. Knopman: Given the presence of SDH in a predominantly older patient population, transradial access is often chosen and preferred, obviating the need to struggle with a difficult arch via a femoral approach. A standard 5-F system is often suitable to enable both roadmap visualization and adequate support for microcatheterization. Guide catheter placement is ideally in the external carotid artery just proximal to the internal maxillary artery. We often image bilaterally to ensure that there are no contralateral collateral vessels supplying a unilateral SDH. In these cases, unilateral embolization is pursued. In cases of initial failure, often a bilateral embolization is performed.

Dr. Arthur: CTA arch anatomy can be very helpful in evaluating whether femoral or radial routes are most favorable for a given patient.[1] At our center, we have moved toward careful evaluation of bilateral vascular supply, as we have found this to be highly variable. This can be used to decide whether unilateral or bilateral embolization makes the most sense.

What are your preferred embolic agents in this setting? What are the key characteristics, sizes, etc?

Dr. Knopman: Embolic agents are often determined by the anatomy/tortuosity of the MMA, as well as the

presence and location of important skull base collateral vessels. Particle embolization is preferred when microcatheterization is placed proximally, as arterial flow is required to carry particles distally. One must ensure the lack of ophthalmic collateral supply in these cases. I prefer 150–250-µm particles, as they are generally too large to penetrate a small collateral but small enough to travel distally into the arterioles of the MMA during embolization. Liquid embolic agents have the benefit of distal penetration and permanence of embolization, as well as the ability to flow retrograde into either contralateral collateral supply or anterior falcine artery supply. This is predicated on being able to place the microcatheter quite distally in the MMA, which can be difficult in tortuous or kinked vasculature. Distal placement also ensures safety from reflux near the skull base collaterals of either the liquid embolic agent or dimethyl sulfoxide (DMSO). The goal of embolization with either particle or liquid agents is to obtain effective embolization of both the frontal as well as the temporal/parietal MMA branches, as they are typically both involved in membrane formation related to SDH (even if the SDH is predominantly focused/located in one particular region of the hemisphere).

Dr. Al-Mufti: I prefer liquid embolic agents due to their ability to completely fill the MMA and allow distal penetration. Although a similar result can be achieved with particles, I believe liquid embolic agents are more durable and offer better visibility than particles and a faster intervention. This may not be a popular belief, but I feel that distal coiling may also be a feasible approach, provided they can be safely deployed in the distal third of the MMA close to the neomembrane using low-profile microcatheters.

Dr. Arthur: Liquid embolics are my preference as this class allows for distal catheterization with smaller catheters, high visibility of the embolysate, and clear demarcation of the extent of reflux.

Dr. Inoa: Most embolic agents that are available on the market have positive reports supporting their use. We have mostly used ethylene vinyl alcohol copolymer because we find it stable and highly radiopaque and are familiar with its behavior. We prefer its lower concentration to achieve easier delivery, greater dispersion, and more distal penetration. Our second choice (outside of a clinical trial) is particles. We use them when general endotracheal intubation is not used, usually due to high anesthesia risks and comorbidities. Particles are also very effective but are less radiopaque than other embolization materials, and their behavior is less predictable; therefore, a very distal microcatheter position with particular attention to potential reflux to collateral branches is critical when particles are used. Small sizes (45–150 µm) are more likely to have distal membrane penetration than bigger-sized (150–200 µm) particles. The efficacy of different-size particles has been reported in case series only.

In the past, when distal navigation into the MMA branches was not possible, we tried embolization with coils alone. We are no longer doing this, as we continue to understand more of the pathophysiology of this condition. To prevent recurrence, the goal of the embolization should target the very small vasculature that supplies the neomembrane. Without distal penetration to these vessels, the procedure is potentially inefficacious; therefore, proximal coiling might not be useful.

What would you hope to see from future device generations, perhaps with specific design for this indication?

Dr. Arthur: I look forward to new catheters that facilitate safer access of the small, tortuous arteries that constitute the distal extent of the MMA branches. I think this—rather than specific characteristics of the embolysate—will be the key to improving safety and efficacy.

How do you approach collaterals when treating SDH?

Dr. Inoa: Although the MMA embolization has been considered a safe and "straightforward" procedure, inadvertent embolization of collaterals is one feared complication. In our practice, patients with ophthalmic collaterals from the MMA or other potentially dangerous anastomoses identified during angiography are not treated. Before any given embolization, we perform careful angiography including the internal carotid arteries (ICAs) and superselective injections. If we identify any extracranial-intracranial anastomosis, we abort the procedure due to its high risk. Another consideration is to avoid penetration of the embolization material into the petrosal branch of the MMA. This is achieved by avoiding significant MMA reflux toward the skull base during the embolization.

Dr. Knopman: It is extremely important to note collaterals to either the ophthalmic artery or petrosal branch of the MMA or rarer collaterals to vasculature of the intracranial posterior fossa. Safe embolization requires distal microcatheterization to these collaterals and avoidance of either DMSO or liquid/particle penetration. It is important to obtain good images of the ophthalmic artery from the ICA (via either common carotid artery or dedicated ICA injection), both to ensure patent and robust native vascular supply as well as to ensure that the MMA does not arise from the ophthalmic artery

itself. This phenomenon is seen in a minority of cases and precludes effective/safe MMA embolization.

What is currently known about embolization as an adjunct to surgical drainage?

Dr. Knopman: Data from large series demonstrate MMA embolization as a surgical adjunct is both safe and effective. Our data suggest that SDH recurrence rates after surgery decrease to < 5% when embolization is performed either shortly before or after surgical evacuation, comparing favorably to historical recurrence rates without embolization. If performed after surgery, it is important to limit craniotomy size so the MMA is not sacrificed during the initial operation, allowing for adequate access to the MMA during subsequent embolization. A burr hole or craniotomy superior to the external acoustic meatus and at/above the superior temporal line is often ideal at preventing surgical sacrifice of the MMA in too proximal a location.

What pitfalls are you most looking to avoid, and how do you ensure this?

Dr. Al-Mufti: Beware of dangerous anastomoses. I try to embolize in each of the branches of the MMA and avoid reflux toward the foramen spinosum.

Dr. Arthur: The most feared complication is nontarget embolization. Inadvertent embolization of the vascular supply to the eye or facial nerve is a well-described complication; in most cases, the operator did not appreciate that there was refluxing embolysate at all during the procedure. This is one of the reasons why I believe that distal catheterization is an important goal for this procedure.

Dr. Knopman: The most important pitfalls to be aware of are the presence of collateral vasculature to functional tissue and safe endovascular access in an elderly population. It is difficult to determine candidacy for safe embolization until endovascular access is first pursued; having a low threshold to aborting the procedure in cases with highly atherosclerotic or difficult access, prominent collateral vessels, or difficulty in obtaining distal MMA catheterization is recommended.

Dr. Inoa: Once careful angiography has been performed to rule out potentially dangerous extracranial-intracranial anastomoses, our goal is to devascularize the membrane with a distal and safe delivery of the embolization material. To achieve distal navigation, a supportive endovascular system should be selected carefully. We often use a 6-F, long sheath and place it in the mid to distal portion of the internal maxillary artery. When this is not possible, an intermediate catheter can be used. Lack of proximal support can overburden the procedure and compromise its effectiveness. In addition, an adequate distal position of the microcatheter will decrease potential unintended reflux into the petrosal branch of the MMA. The petrosal branch origin needs to be identified prior to the embolization, as it supplies the facial nerve and potential anastomoses with the ascending pharyngeal and tentorial arteries could result in complications such as nerve palsies and intracranial embolization.

What are the key ongoing trials in SDH? When are data publications and presentations anticipated?

Dr. Arthur: Here in the United States, David Fiorella and I are leading the STEM investigational device exemption (IDE) trial (NCT04410146), which has enrolled over 250 patients to date. I expect that enrollment will likely be complete in the next 3 to 6 months. I believe the EMBOLISE (NCT04402632) and MEMBRANE (NCT04816591) United States IDE trials are also enrolling well and may finish enrollment this year or next year. There are also ongoing studies in China and in Europe. I would anticipate that we might see results presented toward the end of 2023.

Dr. Inoa: Some of the main trials looking at the safety and efficacy of different embolic materials for MMA embolization for chronic SDH include the following:

- EMBOLISE is a randomized trial including adult patients (age 18-90 years) with symptomatic subacute or chronic SDH. The control arms include surgical drainage versus conservative management, and the intervention arms include surgery plus MMA embolization with the Onyx liquid embolic system (Medtronic) versus Onyx embolization alone. The primary outcome is the effectiveness of the embolization, defined as the incidence of hematoma recurrence or progression requiring reintervention within 90 days postprocedure. The study is currently open and has been recruiting since May 2020.
- STEM is another randomized controlled trial using Squid (Balt), a nonadhesive embolization material for MMA embolization for chronic SDH. The study started in November 2020 and estimates 310 adults (aged > 30 years) enrolled through mid-2024. The study aims to compare embolization alone versus embolization and surgical evacuation (experimental arms) to standard management. The primary outcome is treatment failure, which is defined as reoperation/surgical rescue, reaccumulation/residual SDH ≥ 10 mm, or any stroke, myocardial infarction, or death within 180 days postintervention.

- MEMBRANE is a prospective, multicenter, open-label, randomized controlled trial in which adult patients receive standard of care alone or standard of care plus TruFill n-BCA (Cerenovus) MMA embolization for the treatment of chronic SDH. The primary outcome is effectiveness (SHD recurrence/progression or reintervention) within 180 days. The study started in May 2021 and is recruiting.
- The Middle Meningeal Artery Embolization for Chronic Subdural Hematoma trial (NCT04065113) is a nonrandomized clinical study looking at the safety and efficacy of MMA embolization with polyvinyl alcohol particles for chronic SDH in addition to standard treatments in patients who are not obvious surgical candidates or those with recurrent/refractory hematomas. The outcomes of these patients will be compared to matched historical controls. The trial has been enrolling since September 2019 and estimates 600 participants through early 2025. The primary outcomes include recurrent/refractory SDH with repeated imaging at 24 hours and 7 to 10, 30, and 90 days and the number of patients requiring secondary evacuation surgery (treatment efficacy).

Dr. Knopman: The three key ongoing liquid embolic trials to study the role of MMA embolization in SDH are EMBOLISE, STEM, and MEMBRANE. There are also several smaller trials studying the role of polyvinyl alcohol particles. It is anticipated that these trials will be completed and reported within the next 1 to 2 years. They will be evaluating the role of MMA embolization in both the surgical and nonsurgical patient populations.

What do you predict for the near future of SDH care? What will make or break embolization as a primary treatment option?

Dr. Arthur: When we study diseases where the natural history event rate is low (eg, unruptured aneurysms, arteriovenous malformations), it is difficult to generate unequivocal level 1 evidence for a new therapy. Chronic SDH is a relatively common disease state where the natural history event rate (clinically significant recurrence or residual) is high. This will allow us to really understand a lot about the possible safety and effectiveness of embolization and use the evidence to make better recommendations for patients.

Dr. Al-Mufti: I feel MMA embolization will serve as an adjunct therapy for populations who are at higher risk for reaccumulation after surgery or those too sick to undergo surgery.

Dr. Knopman: MMA embolization holds great promise in decreasing morbidity and recurrence rates associated with the treatment of subacute and chronic SDHs in both the surgical and nonsurgical patient population. Ultimate success in applying this novel treatment modality rests on ensuring its safe application in elderly patients with a focus on complication avoidance and optimal anatomic selection criteria.

Dr. Inoa: The addition of MMA embolization as the standard of care for chronic SDH is currently being studied. Although multiple reports highlight the benefits of this procedure, we need further data that will help us select patients, time the procedures, choose embolization materials, and understand the pathophysiology of this condition. Progress is happening, as one major nonrandomized and at least three randomized prospective clinical trials are underway. With some variation, all trials are looking at the safety and efficacy of this minimally invasive procedure. From prior reports and clinical practice, it seems that the procedure remains safe and straightforward. With good endovascular techniques and understanding of the anatomy, the success of the MMA embolization can be reproducible. As of now, the major question lies on its true efficacy. Patience should be our ally, as it seems that the answer to this important question will be available in 2024 and 2025. In the meantime, we encourage physicians to enroll these patients into the available trials whenever possible—it remains our responsibility to contribute to our field and advance best medical practices. ■

1. Khan NR, Peterson J, Dornbos Iii D, et al. Predicting the degree of difficulty of the trans-radial approach in cerebral angiography. J Neurointerv Surg. 2021;13:552-558. doi: 10.1136/neurintsurg-2020-016448

Disclosures
Dr. Al-Mufti: Member of the steering committee for the MEMBRANE trial.
Dr. Arthur: Coprincipal Investigator for the STEM trial and paid for that work by trial sponsor Balt.
Dr. Inoa: Consultant to Cerenovus, Corindus Vascular Robotics, Medtronic, MicroVention, Inc., Penumbra, Siemens Healthcare, Stryker Neurovascular, and Viz.ai, Inc.
Dr. Knopman: Co-Principal Investigator for EMBOLISE trial and paid for that work by trial sponsor Medtronic.