

Middle Meningeal Artery Embolization for Subdural Hematoma:

What We've Learned, What We Need to Know

The current state of middle meningeal artery embolization for subdural hematoma.

By Joseph A. Carnevale, MD; Gary Kocharian, MD; Jacob Goldberg, MD;
Alexander D. Ramos, MD, PhD; Justin Schwarz, MD; and Jared Knopman, MD

Nonacute subdural hematoma (NASDH) is an increasingly challenging condition to medically and surgically manage due to a variety of factors, most notably its rising prevalence, baseline patient substrate, recrudescence pathophysiology, current treatment paradigms, and the impact on the health care system. NASDH is an extremely common pathology, with an overall incidence of up to 20 persons per 100,000 per year in the general population, and even more so in the elderly population, with up to 74 persons per 100,000 for those aged ≥ 65 years.¹⁻⁷ Considering the overall aging population, the morbidity burden associated with this population, and the increasing use of antiplatelet and anticoagulant medications, it is no surprise why NASDH is already one of the most common neurosurgical conditions, and its incidence is expected to double over the next 25 years.^{6,8-15}

Currently, the gold standard treatment for symptomatic NASDH is surgical evacuation of the hematoma.^{6,11,16} By means of a craniotomy, burr holes, or bedside twist-drill craniostomy, removal of the subdural collection has been the treatment paradigm in neurosurgical practice. For patients unable to undergo surgery or those who have smaller, asymptomatic NASDH, nonsurgical options (eg, steroids, statins, anti-fibrinolytics, angiotensin-converting enzyme inhibitors) have been investigated but without much promise.^{6,17-22} Despite initial surgical and medical treatment, NASDH is notorious for recurrence, further complicating its management. Throughout the literature and neurosur-

gical practice, recurrence of NASDH is widely accepted, expected, and unsuccessfully mitigated notwithstanding dedicated efforts. Despite the countless permutations of surgical treatment strategies, including craniotomy size, drain location, and postoperative patient positioning, NASDH has a variable rate of recurrence of 2% to 37%, with most studies reporting 10% to 20% hematoma recurrence.^{1-4,11,23-31} This means despite an ambulance transfer, emergency department evaluation, hospital admission, operating room evacuation, intensive care unit attention, serial radiographic evaluations, and possible physical/occupation therapy, possibly up to one in three NASDH patients is likely to need to repeat the entire process, resulting in an unprecedented toll on not only the patient but on the overall health care system.

Middle meningeal artery embolization (MMAe) has created a paradigm shift in the care and management of patients with NASDH. This paradigm shift stems from the basic principle that to successfully treat a condition, its pathophysiology must be understood. Despite what is taught in medical school as doctrine—epidural hematoma is to artery as subdural hematoma is to vein—careful examination of NASDH pathophysiology and its recurrence has revealed a more complex interworking, thereby explaining exactly why a novel, outside-the-box approach is needed for this challenging pathology.

Briefly, NASDH and its subsequent recurrence is a pathologic chain reaction beginning with separation of the dural membrane bilayer, thereby triggering

a healing response and dural border cell proliferation. Subsequently, an inflammatory reaction occurs, resulting in granulation tissue formation, macrophage deposition, hyperfibrinolysis, and angiogenesis, which induces neovascularization. Finally, this fragile network of capillaries causes hematologic leakage into the hematoma cavity, resulting in growth and recurrence over time. This process has been uniformly accepted as the true pathophysiology underlying the chronicity, refractoriness, and recurrence of NASDH.^{6,11,16,17,23,25,32-39}

MMAe is a minimally invasive, neuroendovascular procedure that allows for direct access to the main blood supply of the dura, the MMA, and can obliterate the underlying cause of NASDH, halting neovascularization and allowing the collection to be resorbed without recurrence. This article dives into the current state of MMAe in the literature, explores the aspects that require further evaluation, and addresses the next steps toward a major paradigm shift in NASDH management.

CURRENT STATE OF MIDDLE MENINGEAL ARTERY EMBOLIZATION

MMAe was first mentioned 20 years ago in the literature in a Japanese case report.⁴⁰ In many ways, this report highlights the quintessential NASDH patient, with an underlying coagulopathy and numerous recurrences requiring repeated surgical evacuations. On February 22, 1999, the first MMAe took place using polyvinyl alcohol (PVA) particles and without complication. Over the subsequent 7-month follow-up period, the patient experienced no further recurrence and the hematoma resolved.

Salvage MMAe for Refractory NASDH

Over the past 2 decades, clinicians and researchers from around the world have closely examined the clinical impact of MMAe. Subsequent to the aforementioned index MMAe report, a series of case reports defining the well-known problem of NASDH and outlining use of MMAe on an individual basis paved the way to the first low-volume MMAe case series. Despite all of these series having fewer than 10 patients, researchers called attention to the utility of MMAe as an adjunct following recurrent surgical evacuation. Each of these early series examined patients with recurrent NASDH re-presenting with clinically and/or radiographically significant hematomas and discovered impressively low recurrence rates with MMAe compared with the high rate of recurrence with standard of care.⁴¹⁻⁴⁸

In 2017, the first single-institution cohort study retrospectively examined 372 patients with NASDH, 11.6% (n = 43) of whom presented with hematoma recurrence requiring repeat surgical evacuation.³¹

Of the 43 patients who underwent a second craniotomy, 23 followed conventional postoperative care and follow-up, and 20 patients underwent MMAe. At 3-month follow-up, the MMAe group had statistically significant faster brain reexpansion time (34 vs 98 days) and a decreased rate of hematoma recurrence (3.8% vs 33.3%). Despite the obvious drawbacks of this study design and sample size, for patients with refractory operative NASDH, postoperative MMAe proved to be a minimally invasive, low-complication, and effective means to lower NASDH recurrence. In 2018, two larger retrospective case series further established the utility of MMAe as a means for reducing NASDH recurrence rates in patients with a history of one or more surgical evacuations compared with historic controls.^{16,23}

Upfront MMAe

Salvage MMAe for refractory NASDH has been well established, and clinicians have started exploring further applications for this promising procedure. Upfront MMAe offers treatment for previously untreated, nonoperative NASDH in patients who are clinically symptomatic or failed conservative, expectant management. In 2017, Link et al reported the first series of upfront MMAe for previously untreated symptomatic NASDH.⁴⁶ Despite the small patient number, this series introduced MMAe as a treatment alternative to surgery, thereby further establishing MMAe as a safe and minimally invasive treatment strategy for NASDH.

Link et al performed a more robust case series examining upfront MMAe in addition to refractory NASDH and reported a 91% long-term (> 6 weeks) success rate, defined as avoidance of surgery and no procedure-related complications.²³ Subsequently, other research groups demonstrated similar recurrence rates of 0% to 3.7% compared to 27.5% NASDH recurrence for their institutional historical controls following standard of care.^{16,49,50} Interestingly, one group pushed the limits of operative radiographic criteria for subdural hematoma and achieved lower recurrence rates with upfront MMAe than with standard of care in patients with hematoma thickness up to 25 mm and > 5 mm midline shift.⁴⁹

Prophylactic MMAe

For individuals who present with a symptomatic operative NASDH, prophylactic embolization remains another promising application for MMAe. Given the well-known rate of recurrence and supporting pathophysiology for such events, it would stand to reason that newly diagnosed hematomas requiring evacuation should undergo prophylactic MMAe to further halt any chance of future recurrence.

Prophylactic MMAe has been shown in numerous studies to be effective in further decreasing the rate of recurrence of NASDH after first-time hematoma evacuation.^{16,23,51,52} Ban et al and Shotar et al both demonstrated that prophylactic MMAe decreases the NASDH recurrence rate to 4% and 2.2% as compared with a control group recurrence rate of 14% and 27.5%, respectively.^{16,51} Furthermore, the Carnevale et al recently evaluated prophylactic MMAe by evacuation method (craniotomy, burr hole, twist-drill craniostomy) and found MMAe resulted in a recurrence rate of 0% after craniotomy and burr hole for hematoma evacuation, whereas bedside craniostomy resulted in a recurrence rate of only 4.5%.⁵² Prophylactic MMAe has joined upfront MMAe and salvage MMAe as another promising application in the management of NASDH.

Currently, the most robust evidence regarding MMAe and NASDH rests in multicenter case series, systematic reviews, and meta-analyses. Table 1 outlines the population, results, and conclusions for each of these studies.^{6,11,15-17,23,25,31,41-46,49-58} One of the largest multicenter respective series reported nearly 72% hematoma improvement and 6.5% failure rate.¹¹ Moreover, another large multicenter review examined elderly patients with NASDH and their associated morbidity burden; MMAe continued to be effective, with 91% and 98% success rates and 4.6% and 7.8% failure rates for patients aged 65 to 79 and > 80 years, respectively.⁵² Based on meta-analyses in the current literature, hundreds of patients who underwent MMAe have been evaluated, and the conclusions further support MMAe as an integral part of NASDH management. Specifically, not only has the NASDH recurrence rate with MMAe been repeatedly shown to be lower than standard of care (2.1% vs 27.7%), but upfront and salvage MMAe results in recurrence rates below the standard of care (4.1% and 2.4%, respectively).^{17,25} Moreover, patients with NASDH have a 26% chance lower risk of recurrence and a 20% lower need for surgical rescue with MMAe.⁶

Overall, the current body of literature on MMAe has effectively narrowed the recurrence rate of NASDH from 2% to 37% after surgical evacuation to 0% to 4.1%.^{50,59} Nevertheless, these data from case reports, case series, retrospective studies, and meta-analyses have not shifted MMAe into standard of care. The final steps toward a more widely accepted paradigm shift in the treatment of NASDH are underway. Currently, two randomized open-label trials comparing upfront MMAe as well as an adjunctive to surgical evacuation of hematomas are underway, and two open-labeled nonrandomized trials are recruiting patients.⁶⁰⁻⁶² With this necessary next step, there will be more robust evaluation

of the significance of MMAe and hopefully a substantial change in the care of patients with NASDH.

REMAINING QUESTIONS FOR MMAE

One of the most important questions regarding MMAe and its role in NASDH management is whether it will prove to be effective in the gold standard of clinical trials. Although these studies are underway, there are more remaining questions regarding technical aspects and patient selection for MMAe that remain unanswered.

Radial Versus Femoral

Neuroendovascular procedures have long been conducted via femoral arterial access, which remains the primary access point for all diagnostic and interventional procedures. Recently, the endovascular community has utilized both transradial and transulnar approaches with increasing frequency, safety, and success.^{11,58,63-66} In one of the largest series to date, 579 neurointerventional treatments regardless of indication were reviewed and 28% were attempted via a transradial approach (TRA). Although the majority were aneurysmal embolization cases, 19% were embolizations and the researchers concluded that TRA carries a lower complication rate, equitable fluoroscopy time, and greater contrast utilization compared to the transfemoral approach.⁶⁴ Although outcome by access was not directly compared, 12.3% of patient underwent TRA in the largest multicenter MMAe series consisting of 154 embolizations.¹¹ Furthermore, Rajah et al conducted an all-TRA MMAe series of 46 patients, with 95.6% technical success due to radial spasm or vessel tortuosity and a comparable success rate of 89%.⁵⁸ Given the lower complication rates and overwhelming patient satisfaction with TRA, all our embolizations are now conducted with a 5-F sheath and TRA if the patient's vascular anatomy is favorable.

Particles Versus Liquids

The question remains of which embolic material results in the most robust and long-lasting MMAe. Various materials are utilized in neuroendovascular embolization procedures including, PVA, Onyx (Medtronic), N-butyl cyanoacrylate (NBCA), or coils, all of which come in a variety of sizes, consistencies, and viscosities. The majority of studies evaluating MMAe utilize PVA particles (> 150 μ m) for embolization.^{11,23,67} Despite their strong literature presence and cost-effectiveness compared to liquid embolics, PVA penetrates only as distal as the vessel size and flow allow, which can be limited, especially in the elderly population.

TABLE 1. SUMMARY OF STUDIES EVALUATING MMAe FOR NASDH

Authors (Year)	Study Type	Study Population	Results	Conclusion
Hirai et al (2004) ⁴⁵	Retrospective case series	2 patients after evac → MMAe	0% recurrence	Histologic and angiographic findings support MMAe for refractory NASDH to prevent expansion, especially for patients with coagulopathy or taking anticoagulant therapy
Ishihara et al (2007) ⁴³	Retrospective case series	7 patients after evac → MMAe	0% recurrence	MMAe eliminates blood supply to abnormal structure in hematoma cavity and may be a useful for intractable NASDH
Mino et al (2010) ⁴²	Retrospective case series	4 patients after evac → MMAe	0% recurrence	MMAe can be an effective adjuvant procedure in preventing the recurrence of chronic subdural hematoma
Hashimoto et al (2013) ⁴¹	Retrospective case series	3 patients after evac → MMAe	0% recurrence	MMAe is effective for refractory NASDH with a risk of recurrence and an effective therapeutic method to stop hematoma enlargement and promote resolution
Tempaku et al (2015) ⁴⁴	Retrospective case series	5 patients after evac X 2 → MMAe	0% recurrence	MMAe may be a treatment of choice for recurrent NASDH
Link et al (2017) ⁴⁶	Retrospective case series	5 patients upfront MMAe	0% recurrence	MMAe could present a minimally invasive and low-risk initial treatment alternative to surgery for symptomatic NASDH
Kim et al (2017) ³¹	Retrospective cohort study	43 patients after evac presented with recurrence <ul style="list-style-type: none"> • 23 SOC • 20 evac & MMAe 	33% recurrence for SOC; 3.8% recurrence for evac & MMAe	Perioperative MMAe could be offered as the least invasive and most effectual means of treatment for NASDH patients with ≥ 1 recurrences
Link et al (2018) ²³	Retrospective case series	60 cases (49 patients) <ul style="list-style-type: none"> • 50 nonprophylaxis (42 upfront, 8 recurrence) • 10 prophylaxis 	50 nonprophylactic, overall: <ul style="list-style-type: none"> • 8.9% failure • 91.1% success See Carnevale et al ⁵²	MMAe may represent a minimally invasive alternative to surgery for new or recurrent NASDH or as prophylaxis to reduce the risk of recurrence after surgery. Given the encouraging results with a 91% long-term success rate, a large-scale clinical trial is warranted
Ban et al (2018) ¹⁶	Retrospective case series	MMAe ± evac (n = 72) <ul style="list-style-type: none"> • 37.5% (27) MMAe alone • 62.5% (45) evac & MMAe prophylaxis SOC (n = 469)	0% (0/27) recurrence for MMAe alone; 2.2% (1/45) recurrence for evac & MMAe prophylaxis 27.5% (129/469) failure	MMAe has a positive therapeutic effect on NASDH and is more effective than conventional treatment
Matsumoto et al (2018) ¹⁵	Retrospective case series	14 patients after evac presented with recurrence <ul style="list-style-type: none"> • 4 MMAe → evac • 10 SOC 	0% recurrence for MMAe; 20% recurrence for SOC	Hematoma organization is crucial. MMAe is optional treatment for refractory NASDH without organized hematoma. For refractory, organized NASDH, evacuation and membranectomy are useful

TABLE 1. SUMMARY OF STUDIES EVALUATING MMAE FOR NASDH (CONTINUED)

Authors (Year)	Study Type	Study Population	Results	Conclusion
Waqas et al (2019) ⁵⁰	Retrospective case series	8 patients <ul style="list-style-type: none"> 6 upfront MMAe 2 after evac presented with recurrence 	0% recurrence in both groups	MMAe of chronic subdural hematoma is safe and effective for NASDH treatment based on reduced recurrence rate and lack of reported complications
Srivatsan et al (2019) ¹⁷	Meta-analysis	598 patients <ul style="list-style-type: none"> 96 MMAe 502 SOC 	2.1% recurrence for MMAe; 27.7% recurrence for SOC	MMAe is a promising treatment for NASDH; future randomized controlled trials are needed
Carnevale et al (2020) ⁵²	Retrospective case series	41 patients (44 postoperative prophylactic MMAe)	4.5% (2/44) recurrence; 0% craniotomy; 0% burr hole/silver dollar; 4.5% (2) SEPS	Postoperative prophylactic MMAe in the setting of surgical evacuation, either via craniotomy or SEPS, may lower the recurrence rate of NASDH
Gomez-Paz et al (2020) ⁴⁹	Retrospective case series	27 upfront MMAe	3.7% (1/27) failure	Upfront MMAe for NASDH with a thickness up to 25 mm is safe and effective in carefully selected asymptomatic or mildly symptomatic patients even in the presence of a MLS > 5 mm
Joyce et al (2020) ⁵⁵	Retrospective case series	121 elderly patients <ul style="list-style-type: none"> 70 patients (65-79 y) 51 patients (> 80 y) 	For 65-70 y: 91% success, 4.6% failure; for > 80 y: 98% success, 7.8% failure	MMAe can be used safely and effectively as an alternative or adjunctive minimally invasive treatment for NASDH in elderly patients
Shotar et al (2020) ⁵¹	Retrospective case series	<ul style="list-style-type: none"> 89 MMAe (prophylaxis & after evac) 174 SOC 	4% (4/89) failure for MMAe; 14% (24/174) failure for SOC	Postoperative MMAe may reduce the recurrence rate of NASDH with a risk factor of recurrence
Rajah et al (2020) ⁵⁸	Prospective case series	44 patients <ul style="list-style-type: none"> 10.9% recurrence 8.7% perioperative treatment 80.4% upfront 	88.6% (39/44) success; 11.4% (5/44) failure	TRA Onyx MMAe under conscious sedation is safe and effective for NASDH treatment. TRA may be especially useful in elderly patients with numerous comorbidities
Catapano et al (2020) ⁵³	Prospective case series	34 patients (40 MMAe)	<ul style="list-style-type: none"> 8% (3/40) failure No failure when MMAe of both branches 	TRA for MMAe with Onyx is both safe and efficacious. Embolization of both the anterior and posterior MMA branches may be associated with a decrease risk of failed treatment. Future randomized controlled trials and/or large prospective studies are warranted
Rinaldo et al (2020) ⁵⁴	Prospective case series	23 patients (29 MMAe) <ul style="list-style-type: none"> 41.4% (12) postoperative prophylactic MMAe 	93.1% (27/29) success; 6.9% (2/29) failure (same patient)	MMAe may be an effective treatment for NASDH. Randomized trials are needed

TABLE 1. SUMMARY OF STUDIES EVALUATING MMAE FOR NASDH (CONTINUED)

Authors (Year)	Study Type	Study Population	Results	Conclusion
Kan et al (2020) ¹¹	Multicenter case series	138 patients (173 MMAe)	70.8% has > 50% improvement; 31.8% improved clinically; 6.5% required further treatment	MMAe may provide a safe and efficacious minimally invasive alternative to conventional surgical techniques
Scoville et al (2020) ⁵⁷	Multicenter case series	132 patients <ul style="list-style-type: none"> • 76% PVA • 24% liquid (Onyx and glue) 	8.1% failure for PVA; 0% failure for liquid	No significant difference in the type of embolic agent used in obtaining 50% reduction in NASDH or avoiding retreatment. However, liquid embolics appear to reach a 50% reduction in hematoma twice as fast as PVA
Bond et al (2020) ⁵⁶	Systematic review	229 patients with 242 MMAe <ul style="list-style-type: none"> • 36.4% upfront • 59.5% recurrence • 4.1% prophylaxis 	4.5% (11/242) failure	Although many of the published studies to date are retrospective and small, patient outcomes are overwhelmingly favorable, which suggests that MMAe is a highly efficacious alternative or adjunct to surgery for treatment of NASDH
Haldrup et al (2020) ²⁵	Meta-analysis	191 patients <ul style="list-style-type: none"> • 119 MMAe primary treatment • 72 MMAe for ≥ 2 recurrence following evac 	4.1% (5/119) recurrence for MMAe primary treatment; 2.4% (2/27) recurrence for MMAe after evac	MMAe may reduce recurrence rates compared with burr hole craniostomy for both primary and recurrent NASDH. A controlled study is warranted
Jumah et al (2020) ⁶	Meta-analysis	177 patients	MMAe vs SOC <ul style="list-style-type: none"> • 26% lower risk of recurrence with MMAe • 20% lower need for surgical rescue with MMAe 	MMAe appears to be a promising treatment for NASDH, yet drawing definitive conclusions remains limited by paucity of data and small sample sizes. Multicenter, randomized, prospective trials are needed. More extensive research on MMAe could begin a new era in the minimally invasive management of NASDH

Note: Failure is defined as surgical rescue following intervention, recurrence is defined as radiographic or symptomatic recurrence of hematoma, and success is defined as stabilization or resolution of hematoma/symptoms.

Abbreviations: evac, surgical hematoma evacuation; MLS, midline shift; MMA, middle meningeal artery; MMAe, middle meningeal artery embolization; NASDH, nonacute subdural hematoma; PVA, polyvinyl alcohol; SEPS, subdural evacuation port system; SOC, standard of care; TRA, transradial access.

PVA is not radiopaque and requires careful administration so as to not underpenetrate distally or reflux into potentially eloquent branches. Moreover, PVA can be resorbed and therefore leaves the possibility of MMA recanalization and hematoma recurrence. On the other hand, liquid embolic agents, including Onyx and NBCA, can be radiographically monitored, infused into more distal vasculature (possibly in an uncontrolled fashion), and result in a permanent embolization.

Of the few studies comparing embolic material, there is currently no superior agent.^{11,63} Kan et al conducted a multicenter study of 154 consecutive MMAe and found no difference between coils, liquids embolics, liquid embolics and coils, particles, and particles and coils.¹¹ Recently, the largest series primarily examining embolic material in MMAe was published with the same equivocal conclusion. However, this study reported that use of liquid embolics resulted in hema-

toma reduction twice as fast as particles ($P = .008$).⁵⁷ Interestingly, regardless of the material used, the extent of embolization to include both the frontal and posterior branches of the MMA is shown to decrease the rate of hematoma recurrence.⁵³

Patient Selection

As with all surgical procedures, careful patient selection can be the main determining factor in a successful outcome. For the otherwise healthy patient who presents with a symptomatic NASDH and meets operative criteria, there is little question to proceed with an evacuation. The aforementioned evidence may even push the clinician to consider prophylactic MMAe. However, for patients with NASDH but a baseline morbidity precluding surgical evacuation, the question stands as to what approach is best. Today, more patients require antithrombotic medications (antiplatelets and/or anticoagulants) for a variety of reasons, which makes discontinuing them, even briefly, very risky. At the same time, more oncologic patients are living longer and developing NASDH with surgically prohibitive platelet counts. For these populations, MMAe offers an alternative approach to the management of an otherwise operative hematoma. The effectiveness in these populations specifically is yet to be studied, and the efficacy of MMAe in these subgroups unknown. Our group is currently in collaboration with Memorial Sloan Kettering Cancer Center for the first and largest nonsurgical NASDH series of oncologic patients undergoing MMAe alone due to hematologic prohibitory factors, and the preliminary results appear promising.

CONCLUSION

Over the past 20 years, MMAe has become a well-accepted and studied intervention for the management of NASDH. Despite the remaining questions, this minimally invasive, low-complication intervention has been shown to significantly reduce the recurrence rate of a notoriously stubborn neurosurgical pathology. Soon, with the completion of ongoing randomized clinical trials, we will potentially see the paradigm shift in NASDH management to include MMAe and, hopefully, a significant improvement in the care of these patients. ■

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Joseph A. Carnevale, MD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
Disclosures: None.

Gary Kocharian, MD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
Disclosures: None.

Jacob Goldberg, MD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
Disclosures: None.

Alexander D. Ramos, MD, PhD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
Disclosures: None.

Justin Schwarz, MD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
Disclosures: None.

Jared Knopman, MD

Department of Neurological Surgery
Weill Cornell Medicine/NewYork–Presbyterian
Hospital
New York, New York
jak9030@med.cornell.edu
Disclosures: None.