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ABSTRACT

BACKGROUND: Middle meningeal artery embolization is an emerging treatment option for chronic subdural hematomas.

PURPOSE: Our aim was to assess outcomes following middle meningeal artery embolization by different techniques, including in comparison with traditional surgical methods.

DATA SOURCES: We searched the literature databases from inception to March 2022.

DATA SELECTION: We selected studies reporting outcomes after middle meningeal artery embolization as a primary or adjunctive treatment for chronic subdural hematoma.

DATA ANALYSIS: We analyzed the risk of recurrence of chronic subdural hematoma, reoperation for recurrence or residual hematoma, complications, and radiologic and clinical outcomes using random effects modeling. Additional analyses were performed on the basis of whether middle meningeal artery embolization was used as the primary or adjunct treatment and by embolic agent type.

DATA SYNTHESIS: Twenty-two studies were included with 382 patients with middle meningeal artery embolization and 1373 surgical patients. The rate of subdural hematoma recurrence was 4.1%. Fifty (4.2%) patients underwent a reoperation for a recurrent or residual subdural hematoma. Thirty-six (2.6%) experienced postoperative complications. The rates of good radiologic and clinical outcomes were 83.1% and 73.3%, respectively. Middle meningeal artery embolization was significantly associated with decreased odds of subdural hematoma reoperation (OR = 0.48; 95% CI, 23.4–99.1; *P* = .047) compared with surgery. The lowest rates of subdural hematoma radiologic recurrence, reoperation, and complications were observed among patients receiving embolization with Onyx, whereas good overall clinical outcome occurred most commonly with combined polyvinyl alcohol and coils.

LIMITATIONS: A limitation was the retrospective design of studies included.

CONCLUSIONS: Middle meningeal artery embolization is safe and effective, either as a primary or adjunctive treatment. Treatment using Onyx seems to yield lower rates of recurrence, rescue operation, and complications whereas particles and coils produce good overall clinical outcomes.

ABBREVIATIONS: cSDH = chronic subdural hematoma; MMA = middle meningeal artery; PVA = polyvinyl alcohol; SDH = subdural hematoma

Chronic subdural hematomas (cSDHs) are a commonly encountered intracranial pathology, occurring in 1–20.6 per 100,000 person-years.[1] The incidence is expected to rise as the population ages worldwide. Surgical evacuation of the hematoma via burr-hole or craniotomy has remained the mainstay of treatment for many years.[1] However, the rate of recurrence or residual hematoma requiring an additional operation has been reported to be as high as 36.4%.[2]

Recently, there has been increasing interest in using middle meningeal artery (MMA) embolization as a treatment option for

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cSDH, because it targets the suspected underlying pathophysiology of cSDH. Although the mechanisms of cSDH accumulation are not fully understood, neovascularization from the MMA is thought to play an important role in cSDH propagation.[3] Following accumulation of blood, usually from minor trauma, in the potential subdural space, the influx of inflammatory cells and proliferation of damaged dural border cells lead to neomembrane formation,[4] neovascularization of the outer membrane, and recruitment of MMA feeders connecting to these neovessels of the outer membrane. Furthermore, these neovessels are leaky and allow continued exudation of blood products, causing further blood accumulation.[4] Embolizing the MMA to eliminate the blood supply and source of cSDH accumulation has been proposed as both a primary and adjunctive treatment for cSDH,[5] particularly in the elderly who have medical comorbidities and are on antithrombotic medications. However, as an emerging treatment, differences in technical aspects of the procedure abound, including in the choice of embolic agent.[3] Particles, liquid embolic agents, coils, and a combination of these agents have all been tried in MMA embolization with varying results. Currently, there is no FDA approval for any of these agents specifically for this indication, though several industry-sponsored prospective trials are currently underway (NCT04402632, NCT04816591, NCT04065113, NCT04410146; clinicaltrials.gov).

A previous meta-analysis reported low rates of recurrence, surgical rescue, and in-hospital complications associated with MMA embolization; indeed, they were lower than those associated with conventional treatment (either surgery or conservative management).[5] However, the authors were unable to examine technical nuances such as the choice of embolization agent due to insufficient data, and their assessment of MMA embolization as a primary or adjunctive treatment was also self-reportedly limited.[5] Since that time, several additional double-arm studies have been published. Our study aimed to provide an updated meta-analysis to assess the outcomes following MMA embolization, including traditional surgical evacuation, and determine whether specific technical nuances, such as the choice of embolization agent, affect the postprocedural outcomes.

MATERIALS AND METHODS

Search Strategy

The search protocol, including research questions and inclusion and exclusion criteria, was developed a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

We queried the Ovid MEDLINE, EMBASE, Web of Science, and Cochrane Library databases from inception to March 2022 to identify studies reporting outcomes in patients with cSDH treated with MMA embolization (Online Supplemental Data). In addition, the references of included publications were searched manually for other relevant studies. The following keywords were used in combination, "subdural hematoma," "cSDH," "SDH," "middle meningeal artery," "MMA," and "embolization, " to identify relevant articles. The search was limited to articles studying humans with patients 18 years of age or older, and in English.

Studies were included if they were randomized or had an observational prospective or retrospective study design and reported outcomes following MMA embolization in patients with cSDH. There were no restrictions on the size of the cSDH or the clinical status of the patients for inclusion. Both single- and double-arm studies were included. Exclusion criteria included case reports, case series with less than 5 patients, review articles, conference abstracts, animal studies, and non-peer-reviewed publications.

Primary MMA embolization was defined as MMA embolization without surgery. Adjunct MMA embolization was defined as planned MMA embolization with surgery; this could occur before or following surgery, as long as the procedures occurred within 48 hours of each other.

Outcomes

Outcomes were initially analyzed as a single group including both MMA embolization alone and MMA embolization and surgery groups. Further subgroup analysis dividing outcomes between both groups and additionally by the embolization agent was performed.

The primary outcomes of interest were rates of cSDH recurrence and cSDH rescue surgery following MMA embolization. Recurrence was defined as the re-accumulation of cSDH, as defined by the study authors, with or without the need for repeat surgery. Reoperation was defined as the need for surgical evacuation (or re-evacuation) of the cSDH following MMA embolization, either due to recurrence of cSDH or unsatisfactory results from the index procedure.

The complication rate following MMA embolization was also collected, and this included procedural-related complications or general complications that occurred during the follow-up interval, as reported by the study authors. Radiologic outcome at last follow-up was collected and dichotomized as good or poor outcome. A good outcome included >50% hematoma resolution, <10-mm residual hematoma width, or improvement on the last CT scans as defined by the study authors. When available, change in hematoma volume or width between the initial and last follow-up CT was also collected. Clinical outcome was collected and dichotomized as good or poor outcome. A good outcome included MR spectroscopy 0–2, Glasgow Outcome Score 4–5, Glasgow Outcome Scale-Extended 5–8, and improvement in neurologic or functional status or neurologic deficit at the last follow-up.

Data Extraction

The following data were extracted from each study: study design, country of origin, patient eligibility, inclusion/exclusion criteria, sex and age of patients, medical comorbidities, presenting neurologic status, presenting size of the cSDH, indication for MMA embolization, primary or adjunctive use of MMA embolization, and embolic agent. In addition, the outcomes of recurrence rates, surgical rescue, complications, radiologic outcome, and clinical outcome were also extracted.

Evaluation of Quality and Risk-of-Bias Assessment for Individual Studies

The Newcastle-Ottawa Quality Assessment Scale Case-Control Studies tool was used after modification to assess the risk of bias in our included studies. The quality of all eligible studies was evaluated independently and in duplicate by 2 reviewers (J.C.K. and M.A.E.), using the 2011 Oxford Center for Evidence-Based Medicine levels of evidence.

Statistical Analysis

All studies that reported outcomes following MMA embolization in patients with cSDH were pooled for meta-analysis of outcomes via pooled weighted proportions or pooled weighted means for continuous outcomes. The results were pooled using ORs in studies that compared outcomes in MMA embolization versus surgery versus conservative management. Additional analyses were performed for MMA embolization as a primary or adjunctive treatment and to compare embolization approaches.

The Q-statistics test and calculation of I^2 were used to assess heterogeneity between studies. P values $< .05$ and I^2 values of $>50\%$ were defined as significant heterogeneity between studies. Pair-wise and subgroup meta-analyses were performed using a random effects model using the Freeman-Tukey transformed proportion and the DerSimonian-Laird approach. A P value $< .05$ was set for statistical significance. Assessment for risk of publication bias was performed using the Egger regression test for funnel-plot asymmetry for all variables that included data from $\geq$10 studies. If the Egger regression test demonstrated that there was a significant risk of publication bias ($P < .05$), the trim-and-fill approach was used to calculate the adjusted value. The meta-analysis was performed by using the OpenMeta-Analyst open source software (https://abstracts.cochrane.org/2010-keystone/openmeta-analyst-open-source-cross-platform-software-advanced-meta-analysis) and the MAJOR tool (metafor package) of Jamovi R-based statistical software (https://www.jamovi.org/).

RESULTS

Search Results

The search strategy returned 536 total and 291 deduplicated results, as seen in the PRISMA diagram (Online Supplemental Data). Following abstract screening and full-text review, 22 articles were included for analysis (Online Supplemental Data),[6-27] totaling 382 patients who underwent MMA embolization, compared with 1373 patients who underwent surgery. Overall, 133 of 757 (17.6%) patients had bilateral SDHs. The mean follow-up ranged between 2 and 26.3 months among studies. Three studies did not report any information on follow-up (Online Supplemental Data).

Study Characteristics

All studies included for analysis were case series, retrospective reviews, or prospective studies compared with a retrospective cohort. There were no prospective randomized trials. All retrospective studies were graded as level 4, and prospective studies with historical controls were graded as level 3, based on the Oxford Center for Evidence-Based Medicine 2011 levels of evidence. The risk of bias was low in 7, moderate in 14 studies, and high in 1 study. Twenty studies were retrospective, and 2 were prospective. The smallest study included 5 patients, and the largest included 138 patients (Online Supplemental Data). Thirteen studies with 457 patients reported the outcomes stratified by treatment technique, 9 studies with 243 patients reported outcomes of patients receiving embolization only, and 10 studies reported outcomes of 278 patients undergoing combined surgery and embolization. Nine studies with 431 patients had no outcomes separated by treatment technique. Overall, 7 studies reported the outcomes of patients receiving embolization with polyvinyl alcohol (PVA); 4, with *n*-BCA; 3, with PVA ± coils; and 2, with Onyx (Medtronic) embolization.

Single-Arm Overall Outcomes

Overall, 397 of 421 (96%; 95% CI, 93.4%–98.7%) patients demonstrated intraprocedural complete embolization of the MMA (Online Supplemental Data). The rate of subdural hematoma (SDH) recurrence was 4.1% (95% CI, 2.8%–5.4%) in 50 of 898 patients following MMA embolization (both primary and adjunct treatment) (Online Supplemental Data). On person-time analysis, the rate of SDH recurrence over time was 0.6% (95% CI, 0.3%–1%) per month (Online Supplemental Data). Fifty of 888 patients (4.2%; 95% CI, 2.9%–5.5%) underwent a reoperation for a recurrent or residual SDH (Online Supplemental Data). Thirty-six of 890 patients (2.6%; 95% CI, 1.2%–3.9%) experienced postoperative complications (Online Supplemental Data). These included 2 groin complications (1 groin hematoma, 1 femoral artery occlusion), 3 procedural complications (rupture of the MMA, 1 transient bradycardia during embolization), 4 postprocedural infarcts (clinical or radiologic), 10 medical complications (urinary tract infection, pneumonia, deep vein thrombosis, pulmonary embolism), and 15 seizures or new neurologic deficits or complications otherwise not specified.

The rates of good radiologic and clinical outcomes were 83.1% (382 of 518; 95% CI, 74.6%–91.5%) and 73.3% (292 of 372; 95% CI, 60%–86.6%), respectively (Online Supplemental Data). On follow-up, the SDH volume decreased with a mean reduction of 54.2 mL (95% CI, 46.3–62 mL) (Online Supplemental Data) and a mean reduction in SDH width of 9.9 mm (95% CI, 7.5–12.2 mm) (Online Supplemental Data).

Embolization Alone versus Adjunct to Surgery

The rates of SDH recurrence were comparable between patients who received embolization only (6.3%; 95% CI, 3.3%–9.3%) and those who received a combination of embolization and surgery (5.3%; 95% CI, 2.7%–7.9%; $P = .976$). On person-time analysis, the risk of SDH recurrence during follow-up in the embolization-only group was 1.7% (95% CI, 0.7%–2.6%) per month compared with 0.3% in the combined embolization and surgery group (95% CI, 0%–0.6%; $P = .035$). SDH reoperation was required in 5.4% (95% CI, 2.6%–8.2%) of patients undergoing embolization alone and in 4.6% (95% CI, 2%–7.2%; $P = .912$) of patients with combined embolization and surgery. Eight (2.2%; 95% CI, 0.4%–4%) of 243 patients with embolization alone and 22 (5.5%; 95% CI, 1.5%–9.5%; $P = .025$) of 280 patients with combined embolization and surgery experienced postoperative complications. Good radiologic resolution was reported in 94.1% (95% CI, 84.8%–

100%) of embolization alone and in 92.1% (95% CI, 85.8%–98.5%; $P = .187$) of combined embolization and surgery cohorts. Rates of good clinical outcomes were similar in the embolization alone (81.2%; 95% CI, 66.7%–95.6%) and combined embolization and surgery groups (75.3%; 95% CI, 36%–100%; $P = .569$).

Embolization Comparing Agent Choice

SDH recurred with a rate of 4.7% (95% CI, 1.5%–8%) in patients treated with PVA, 3.5% (95% CI, 0%–8.1%) with *n*-BCA, 2.2% (95% CI, 0%–5.1%) with PVA ± coils, and 2% (95% CI, 0%–6.4%) in patients receiving Onyx. The SDH reoperation rate was 4.2% (95% CI, 1.2%–7.3%) for PVA, followed by 4.1% (95% CI, 1%–7.3%) for PVA ± coils, 3.7% (95% CI, 0%–8.2%) for *n*-BCA, and 2% (95% CI, 0%–6.4%) in patients receiving Onyx. The rate of complications was 5.6% (95% CI, 1.1%–10.1%) for PVA, 3% (95% CI, 0%–6.9%) for *n*-BCA, 2% (95% CI, 0%–6.4%) in patients receiving Onyx, and 1.4% (95% CI, 0%–3.7%) in patients receiving PVA ± coils. Good radiologic outcomes were similar comparing embolization agents (Onyx: 82%; 95% CI, 57%–100% versus PVA ± coils: 84.4%; 95% CI, 63.9%–100%). Rates of good clinical outcomes were 85.2% (95% CI, 68.1%–100%) for PVA ± coils, 78.5% (95% CI, 55.9%–100%) for *n*-BCA, and 75.7% (95% CI, 63.8%-87.5%) in patients receiving Onyx. Detailed outcomes by treatment technique and embolization agent are available in the Online Supplemental Data.

Pair-Wise Meta-analysis Outcomes

On a pair-wise meta-analysis, there was no significant difference between MMA embolization alone and combined surgery with MMA embolization in terms of SDH recurrence (OR = 0.36; 95% CI, 0.12–1.09; $P = .071$). MMA embolization alone significantly decreased the odds of SDH reoperation (OR = 0.48; 95% CI, 23.4–99.1; $P = .047$) compared with surgery alone. No other significant differences were noted in other safety, radiologic, and clinical outcomes. Detailed outcomes of the 2-arm meta-analysis by treatment technique and embolization agent is available in the Online Supplemental Data.

Heterogeneity and Risk of Bias

Among the results of single-arm meta-analysis, high heterogeneity ($I^2 > 50\%$) was noted in the following outcomes: good radiologic outcomes (85.03%), good clinical outcomes (92.37%), and SDH width decrease (93.99%). Among pair-wise meta-analysis outcomes comparing MMA embolization with combined MMA embolization and surgery, there were good radiologic ($I^2 = 94.51\%$) and good clinical ($I^2 = 51.01\%$) outcomes; and among those comparing MMA embolization with conservative treatment, SDH reoperation outcome ($I^2 = 88.16\%$) showed high heterogeneity. A sensitivity analysis was performed taking into consideration the embolization agent used or by exclusion of individual studies thought to be the source of heterogeneity. Grouping good radiologic outcomes by treatment type led to a decrease in I^2 to null, supporting this as a reason for the high heterogeneity (Online Supplemental Data). I^2 for good clinical outcomes decreased from 93.37% to 71.81% and 64.98% following stratification of outcomes by treatment and embolization agent, respectively. Three studies were identified as main sources of heterogeneity, including Enriquez-Marulanda et al,[10] Okuma et al,[20] and Waqas et al,[26] which may relate to their inclusion of different treatment approaches (both embolization and combined) and different embolization agents (PVA and PVA+ coils). Following exclusion of these studies, I^2 decreased to 21.38%, and the rate of good clinical outcomes increased from 73.3% (95% CI, 60%–86.6%) to 87.8% (95% CI, 83.2%–92.5%). The low number of studies (2–3) included in the pair-wise meta-analyses (good radiologic and clinical outcomes after MMA embolization compared with a combined approach, SDH reoperation outcomes after MMA embolization versus conservative management, and SDH width outcomes) was thought to be the main source of heterogeneity.

Publication bias was determined to be present for only good radiologic outcomes (83.1%; 95% CI, 74.6%–91.5%; P value = .0023) (Online Supplemental Data). The adjusted outcome based on the trim-and-fill approach was 73.9% (95% CI, 59.1%–86.7%).

DISCUSSION

Our systematic review and meta-analysis summarize the most recent literature reporting MMA embolization for patients with cSDH in comparison with surgical interventions and draw attention to the importance of the choice of embolization agent for treatment success, in addition to the baseline patient clinical status, anatomic variations of the MMA, and experience of the neurointerventionalist. Most patients receiving MMA embolization achieved good clinical outcomes with an excellent rate of good radiologic outcomes and low recurrence and reoperation rates. There were no differences in outcomes comparing embolization-only and combined embolization with surgery except for reoperation and complication rates, which were significantly higher in the combined approach. Patients receiving embolization via PVA accompanied by coils had relatively improved radiologic (84.4%) and clinical outcomes (85.2%) but slightly higher reoperation rates (4.1%), whereas patients embolized with Onyx had the lowest rates of SDH recurrence (2%), reoperation (2%), and complications (2%).

Surgical evacuation of cSDH is associated with high rates of recurrence and complications.[28] Therefore, it may be a less desirable option for elderly patients with poor baseline clinical status and significant underlying comorbidities. On the other hand, it may also be unnecessary for patients with favorable clinical and radiologic status.[29] The use of less invasive treatment based on a better understanding of the pathophysiology of SDH will likely improve the outcomes. Thus, surgical evacuation may be reserved for those likely to benefit most, highlighting the need for optimization of treatment selection. Embolization of the MMA has gained considerable popularity in the past 2 decades.[6,14,26] Most patients having undergone MMA embolization in this study achieved excellent clinical and radiologic outcomes, compared with the surgery cohort.

MMA embolization and surgery could have synergistic goals when used in a combined approach appropriately for patients with mass-effect symptoms. Surgery can alleviate those symptoms, whereas MMA embolization can decrease the recurrence of SDH. However, we did not observe a significant difference between the 2 approaches (MMA embolization alone versus MMA embolization with surgery) in these outcomes. This result may be due to selection bias related to the retrospective nature of most of the included studies, in which patients undergo embolization alone or embolization with surgery based on their clinical presentation and the operator's decision-making. Furthermore, considerable heterogeneity exists in follow-up periods among studies, which was validated by the significant difference in the SDH recurrence rate per month between MMA embolization alone (1.7%/month) and combined embolization and surgery (0.3%/month). Thus, the combined approach might be associated with better radiologic outcomes but was not found to positively affect the clinical outcomes in this study. Unsurprisingly, this combined approach might add more morbidity related to the higher complication rates (5.5%) reported compared with embolization alone (2.2%). The 2-stage nature of the combined approach explains the higher complication rate of embolization accompanied by surgery because each procedure has its own risks.

Reoperation rates were lower in the MMA embolization cohort compared with surgery alone, emphasizing the role of embolization in decreasing the overall morbidity in elderly patients and efficacy in the management of cSDH. Covariates, such as age, hematoma side (unilateral, bilateral), and other hematoma characteristics, and clinical comorbidities play a crucial role in the selection of the optimal treatment for cSDH. The choice of embolization agent is a crucial factor that was demonstrated to affect outcomes on the basis of experimental and a few observational studies. Shapiro et al,[3] in a comprehensive review of the pathoanatomy of SDH, summarized the theoretic advantages and disadvantages of different embolization agents. PVA may have better penetration distally but higher recurrence rates compared with liquid agents, related to delayed recanalization. Liquid agents, such as Onyx or *n*-BCA, may be associated with a lower penetration profile but a more stable occlusion. Furthermore, coils are highly thrombogenic and can be deployed, commonly into the more proximal artery, along with PVA, leading to a more stable and permanent occlusion.

Operator experience and comfort level with a specific embolic agent also play a role in its safety and efficacy. Rates of radiologic and clinical outcomes of patients receiving MMA embolization were comparable among the embolization agents. However, high recurrence rates were reported after PVA alone but not with PVA and coils, emphasizing the benefit of combining agents to achieve better stability. Most interesting, reoperation was noted to be slightly higher in patients treated with PVA alone but also in those treated with PVA and coils. PVA was nonsignificantly associated with a slightly higher complication rate. This finding warrants further study but may be related to its higher risk of penetrating into collaterals, such as those to the ophthalmic artery. Across all agents, Onyx was associated with the lowest recurrence, reoperation, and complication rates.

Conservative care with observation and medical management may be preferable for patients with an asymptomatic presentation or those with very severe symptoms and poor baselines in which neither surgery nor MMA embolization is likely to offer benefit.[30] Catapano et al,[30] in a propensity-adjusted comparison of 35 patients receiving MMA embolization versus 196 patients treated conservatively, reported no difference in clinical outcomes; however, conservative treatment was much more commonly associated with treatment failure (OR = 13; 95% CI, 1.7–99; $P = .01$) and incomplete hemorrhage resolution (OR = 5.4; 95% CI, 2.5–12; $P < .001$). Still, data available about outcomes of conservative management compared with MMA embolization are scarce, and further studies are warranted. Furthermore, treatment-selection criteria must be better defined on the basis of clinical status and radiographic characteristics. Thus, large multicenter cohort studies stratifying outcomes after these different approaches (MMA embolization, surgery alone, combined approach, and conservative approach) by anatomic characteristics of SDH and baseline clinical characteristics are needed to identify the patient-specific optimal treatment and develop clinical treatment guidelines.

Limitations

As with most systematic reviews and meta-analyses, this study was limited by the number of studies meeting the inclusion criteria and the quality of those studies. There were no randomized controlled trials. Nevertheless, this does represent the largest cohort of patients studied to date. Additionally, our meta-analysis showed considerable heterogeneity in several outcomes, particularly clinical and radiologic outcomes, which had additionally low report rates, with only 11 of 22 studies reporting their outcomes. This considerable heterogeneity was likely due to heterogeneous procedural details (embolization alone versus combined treatment, choice of different embolic agents), so while these outcomes provide a broad overview of the potential for MMA embolization, the outcomes from the additional analyses comparing agents may be more applicable to specific patient situations. There may also be substantial variations among individual studies with regard to treatment selection for MMA embolization versus surgery alone versus a combined approach. Patients undergoing surgery may have more severe symptoms based on cSDH mass effect requiring decompression. We were unable to assess the effect of this variable on postprocedural outcomes, and future clinical trials should consider this for patient treatment selection.

CONCLUSIONS

MMA embolization appears to be a safe and effective intervention for cSDH, either as a primary or adjunctive treatment. The combined approach may be best used for patients with large hemorrhages to alleviate mass effect while decreasing the risk of recurrence. PVA alone may have higher rates of recurrence, but the addition of coils with PVA improved stability rates. Embolization using Onyx seems to lead to lower rates of recurrence, rescue operations, and complications. Further large multicenter studies and randomized trials evaluating safety, radiologic outcomes, and clinical outcomes are warranted to better understand the characteristics associated with the benefit of different embolization agents and to set updated management guidelines for the treatment of cSDH.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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