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Embolization of the Middle meningeal artery in chronic subdural hematoma — A systematic review

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A B S T R A C T

Chronic subdural hematomas (cSDH) are one of the most frequent reasons for consultation in neurosurgery. Multiple authors have proposed middle meningeal artery embolization (MMAE) as an option in cSDH patients to manage recurrence or avoid surgery altogether. Although many articles have been published on the matter, the current body of evidence still has to be evaluated before MMAE is integrated into clinical practice.

The goal of this study was to review the evidence on MMAE in cSDH to assess its safety, feasibility, indications and efficacy.

We performed a systematic review of the literature according to PRISMA guidelines using multiple electronic databases.

Our search yielded a total of 18 original articles from which data were extracted. A total of 190 patients underwent MMAE from which 81.3% were symptomatic cSDH. Over half (52.3%) of the described population were undergoing antithrombotic therapy. Most (83%) procedures used polyvinyl alcohol (PVA) particles and no complications were reported regarding the embolization procedures. Although the definition of resolution varied among authors, cSDH resolution was reported in 96.8% of cases.

MMAE is a feasible technique for cSDH, but the current body of evidence does not yet support its use as a standard treatment. Further studies with a higher level of evidence are necessary before MMAE can be formally recommended.

1. Introduction

Chronic subdural hematomas (cSDH) have an incidence of up to 58.1 per 100 000 person-year in patients over 65 years old and often require neurosurgical attention [1]. Traditionally, cSDH are treated through burr hole evacuation and irrigation, however recurrence is frequent and ranges from 11 to 37% [1–3]. The prevalence of recurrence is over-represented in patients undergoing antithrombotic therapy [4,5]. A recent meta-analysis found that anticoagulated patients had over twice the risk of recurrence compared to patients not taking any antithrombotic medication, whereas another study found that patients on antiplatelet therapy had 4 times the risk [4,5]. Hence, in patients affected with a cSDH, the resumption of antithrombotic medications is usually not considered safe until the hematoma has resolved [6].

The pathophysiology of cSDH involves the formation of neo-membranes from dura mater inflammatory remodeling. This distinguishes cSDH from acute SDH and led to the recent suggestion that cSDH should rather be called *membrane-associated SDH* [7]. The membrane and newly formed capillaries are fed through the dura mainly by distal branches of the middle meningeal artery (MMA) [8]. Strategies tested to non-invasively address this growth have included dexamethasone [3] as well as tranexamic acid [9]. Recently, several case reports and two prospective studies suggested that embolization of the MMA could inhibit the influx of blood into this membrane and thus prevent the accumulation of the hematoma in the subdural space [10–12]. The goal of this study was to systematically review all published cases of MMA embolization (MMAE) in cSDH to assess the procedure's safety, feasibility, indications and efficacy.

2. Materials and methods

2.1. Study design and search strategy

We performed a systematic review according to the PRISMA guidelines [13]. An electronic literature search on the 12th of August

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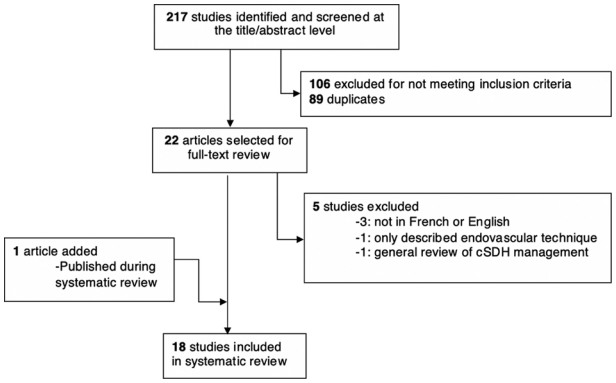

Fig. 1. Flowchart diagram of the study selection process.

2018 was performed on Medline, Pubmed and Scopus for indexed studies, using and combining the main following key concept terms: "chronic subdural hematoma", "embolization" and "middle meningeal artery". Detailed search strategy design is available upon request. A final search was performed the 9th of November 2018 and any supplemental articles meeting the inclusion and exclusion criteria were included in the final results (Fig. 1 and Table1).

A meta-analysis was not performed for the several reasons. Information regarding the indication, the timing, as well as the definition of cSDH treatment success was found to be heterogeneous, which renders a more detailed analysis of variables impossible. Moreover, the information regarding said variables was not always available in the included papers. Furthermore, the level of evidence available and the inclusion of many case studies renders a meta-analysis less relevant.

2.2. Selection criteria

We considered all studies from the period of January 1st, 1980 through November 2018 that met the criteria listed in Table 2.

2.3. Study selection

Articles identified through the electronic literature search were independently screened on the basis of the title and abstract by two reviewers (J.C., a second-year radiology resident and C.T., a third-year neurosurgery resident). The reviewers verified whether inclusion and exclusion criteria were met, and for any article that had any potential for study inclusion, the full text was further retrieved and reviewed in detail by one reviewer (J.C.) to further assess the eligibility of the study. Reasons for exclusion were documented for each article. In order to identify any potential pertinent studies that may have been missed using the above-mentioned procedure, one reviewer (J.C.) crosschecked the reference lists of all the identified studies using this search strategy, until no further articles were identified.

2.4. Quality assessment

The quality of evidence presented by each individual article was graded according to the GRADE guideline [14] and is reported in Table 3.

2.5. Data extraction & analysis

Data extraction was performed by one reviewer (J.C.), using a predefined data extraction form. Study design and methodology, sample population and size, patient baseline characteristics, antithrombotic use, management strategy including medical, surgical and

Table 1
Inclusion and exclusion criteria.

	Inclusion	Exclusion
Patient	Adult patient (> 18 years old) treated for the first time by embolization of the MMA from January 1 st, 1980 to November 9th, 2018 for cSDH.	Adult patient (> 18 years old) treated for a pathology other than cSDH such as: • AVM • DAVF • Neoplasia Pediatric patients (< 18 years old) Early follow-up of patients better described in another paper
Intervention	Any combination of treatment for cSDH that included at least one MMAE and: • Conservative treatment • Medical management • Burr hole or craniotomy evacuation	• Patients who did not undergo MMAE for cSDH. • Technical note or paper assessing only technique safety and/or efficacy
Study design	Original series of at least 1 case of MMAE published in any peer-review journal from January 1st, 1980 to November 9th, 2018 and that includes the following criteria: • French or English language • Prospective or retrospective study with at least one clinical and/or radiological follow-up post-MMAE • Studies from the same author or group if the patients included in the study are different than the ones in previous publications	• Animal studies, opinion papers, commentaries, editorials, systematic reviews, meta-analyses.
Outcome	Any outcome including but not limited to: • Survival • Neurological • Functional (eg.: Ambulatory, ADL) • Quality of life • Radiological • Resumption of medication • Unplanned reoperation/re-embolization Any complications (not limited): • Infection • Rebleeding/recurrence of hematoma • Stoke • Hematomas (any) • HSD recurrence • Surgical rescue	

Table 2
Summary of evidence of MMA embolization — design of included studies.

Author, year	Study type	Patient (Nb)	Age (Mean)	Sex (M: F)	CSDH side (unilateral: bilateral)	Symptomatic Nb (%)	Antithrombotic regimen			Reversal (%)
							Any Nb (%)	OAC (Nb (%)	Anti-platelet Nb (%)	
Mandai et al., 2000 [15]	Case report	1	59	1:0	0:1	1 (100)	0	0	0	NA
Hirai et al., 2004 [16]	Case series	2	72	2:0	1:1	2 (100)	2 (100)	2 (100)	0	100
Ishihara et al., 2007 [17]	Case series	7	NA	NA	NA	NA	NA	NA	NA	NA
Mino et al., 2010 [18]	Case series	4	73	4:0	4:0	NA	NA	NA	NA	NA
Tsukamoto et al., 2011[19]	Case report	1	64	1:0	0:1	1 (100)	NA	NA	NA	NA
Hazra et al., 2011 [20]	Case series	2	NA	NA	NA	NA	NA	NA	NA	NA
Hashimoto et al., 2013 [21]	Case series	5	71.4	3:2	4:1	NA	1 (20)	1 (20)	0	0
Chihara et al., 2014 [22]	Case series	3	67	3:0	NA	NA	NA	NA	NA	NA
Yamamoto et al., 2015 [23]	Case report	1	63	1:0	1:0	1 (100)	NA	NA	NA	NA
Tempaku et al., 2015 [24]	Case series	5	83	4:1	5:0	NA	1 (20)	1 (20)	0	NA
Kang et al., 2015 [25]	Case report	1	13	1:0	1:0	1 (100)	0	0	0	NA
Kim et al., 2017 [26]	Case series	20	74	14:6	14:6	NA	9 (45)	3 (15)	6 (30)	100
Link et al., 2017 [[1]]	Case series	5	66.8	1:4	3:2	5 (100)	5 (100)	0	5 (100)	100
Matsumoto et al., 2017 [27]	Case series	5	68.2	5:0	NA	5 (100)	1 (20)	0	1 (20)	100
Matsumoto et al., 2017 [10]	Case report	1	45	1:0	1:0	1 (100)	NA	NA	NA	NA
Link et al., 2018 [29]	Case series	6	64.5	5:1	5:1	6 (100)	3 (50)	1 (17)	2 (33)	NA
Ban et al., 2018 [12]	Prospective Cohort	72	69.3	48:24	53:19	45 (63)	29 (40)	NA	NA	0
Link et al., 2018 [11]	Prospective Cohort	49	69	32:17	38:11	49 (100)	39 (80)	6 (12)	33 (67)	NA
Total		**190**	**66.8**	**126:55**	**130:43**	**117 (81.3)**	**90 (52.3)**	**14 (14)**	**47 (47)**	**29.4**

endovascular treatment, outcome measures and time at which outcome measures, complications, as well as subdural hematoma recurrence rate and the need for subsequent surgery were collected and analyzed.

3. Results

Our search strategy yielded 217 articles. Of those, 89 were duplicates and 106 were excluded based on their abstract not meeting selection criteria. Twenty-Two English articles were selected for full-text review and 5 more articles were excluded (Fig. 1). No additional studies in French or in English were found in the reference lists of these reports. One article which was published in November 2018 was added after the initial literature search [11]. Eighteen articles were included in the final analysis, including two prospective uncontrolled study, 11 case series (> 1 patient) and 5 case reports involving 1–72 patients per series (Table 2) [1,11,12,15–29]. The level of evidence regarding MMAE efficacy was majorly graded as "very low" in which three articles were graded as "low" (Table 3).

3.1. Demographics

A total of 190 patients underwent MMA embolization in the selected studies (Table 2). The median age was 66.8 years old and 69.6% of these patients were male. From the available data, 130 patients suffered from unilateral cSDH while 43 patients had bilateral cSDH. At the time of cSDH diagnosis, 52.3% of patients were treated with antithrombotic medication, 81.3% of patients were symptomatic and 29.4% of patients had their antithrombotic regimen either reversed or stopped. The type and proportion of antiplatelet or anticoagulant regimens were not systematically reported.

3.2. Treatment paradigm

Sixty-four (33.7%) patients underwent MMAE as a primary treatment of cSDH, including 27 (38%) of the 72 patients in the prospective study by Ban et al. [12], 5 patients (100%) in the *Link et al.* case series published in 2017 [1] and 32 patients (65%) in the latest Link et al. case series [11] (Table 3). A total of 63 (33%) MMAE were performed preoperatively after 1–3 recurrences, followed by a surgical drainage, and 63 (33%) were also performed postoperatively after 1–3 recurrences (Table 3). The indications to treat cSDH using MMAE based on signs and symptoms were not systematically reported and, in general, primary MMAE was reserved for "mildly" symptomatic patients. Link et al. [1] described the first series of five patients whose symptoms ranged from headaches, cognitive decline, gait instability, drift to weakness and who successfully underwent primary MMAE. The details of embolization agents were not systematically described; however, most patients underwent MMAE with polyvinyl alcohol (PVA) particles (83%), followed by n-butyl-2-cyanoacrylate (NBCA) (9%), coils (3%). The side of MMAE with respect to the side of surgery and the type of anesthesia used were not systematically reported.

3.3. Complications

Patients were followed for a period varying from 3 weeks and 5 years, for a median period of 6 months (Table 3). Most importantly, no mortality was reported within the selected articles. Complications were not systematically reported. Interestingly, no complications were reported secondary to MMAE, and only two articles reported any complications, accounting for an overall complication rate of 3.6% [23,26]. One paper reported two surgery-related complications such intracranial bleeding and wound hematoma secondary to the surgical evacuation of the cSDH, and three medical complications such as angina pectoris, pneumonia and delirium; however, the exact complication in a specific subgroup of patients was not detailed [26]. One article reported a subdural empyema due to *Propionibacterium acnes* in a patient that

Table 3
Summary of evidence of MMA embolization - outcomes of included studies.

Study	MMAE			MMAE agent	CSDH resolution definition	Resolution (%)	Complications (Nb)	CSDH recurrence Nb (%)	Follow up (median)	Quality of evidence (GRADE)
	Primary Nb (%)	Pre-operative Nb (%)	Post-operative Nb (%)							
Mandai et al. [15]	0	0	1 (100) (after many recurrences)	PVA	Complete resolution at end of follow up	100	0	0	7 months	Very low
Hirai et al. [16]	0	0	2 (100) (after 2 recurrences)	PVA & coils	No growth	100	NA	0	NA	Very low
Ishihara et al. [17]	0	0	7 (100) (after 2-3 recurrences)	NBCA	NA	100	NA	0	15 months	Very low
Mino et al. [18]	0	2 (50) (after 1-2 recurrences followed by drainage)	2 (50) (after 1-2 recurrences)	Gelatin sponge & coils	No recurrence or enlargement	100	NA	0	6 months	Low
Tsukamoto et al. [19]	0	0	1 (100) (after 3 recurrences)	PVA	NA	0, stable	NA	0	18 months	Very low
Hazra et al. [20]	0	0	2 (100) (after 2 recurrences)	PVA	NA	50	0	1 (50) (1 pt remained symptomatic & required craniotomy)	6 months	Very low
Hashimoto et al. [21]	0	1 (20) (after 2 recurrences and before 3rd irrigation)	4 (80) (after 1-2 recurrences)	NBCA & PVA	NA	100	NA	0	NA	Very low
Chihara et al. [22]	0	1 (33) (after 2 recurrences, followed by drainage)	2 (67) (after 2-3 recurrences)	PVA & coils	NA	66.7	NA	1 (33.3) (1 pt required craniotomy 3 months post MMAE)	6 months	Very low
Yamamoto et al. [23]	0	0	1 (100) (after 2 recurrences)	NBCA	NA	0	Infected subdural hematoma	1 (100) (1 pt required 3rd burr hole followed by craniotomy)	2 years	Very low
Tempaku et al. [24]	0	4 (80) (after 2-3 recurrences, followed by drainage)	1 (20) (after 2 recurrences)	PVA & coils	No recurrence of hematoma	100	0	0	17.6 weeks	Very low
Kang et al. [25]	0	0	1 (100) (after 1 recurrence)	coils	NA	100	0	0	5 years	Very low
Kim et al. [26]	0	4 (25) (after 1 recurrence, followed by drainage)	16 (75) (after 1 recurrence)	PVA	Near total resolution & clinical status	95	2 surgical & 3 medical	1 (5) (1 pt SDH eventually spontaneously regressed)	6 months	Very low
Link et al. [1]	5	0	0	PVA	Volumetric reduction	100	0	0	3-14 weeks	Very low
Matsumoto et al. [27]	0	5 (100) (after 2-3 recurrences followed by drainage)	0	NBCA & coils	Complete resolution on follow up CT	100	0	0	3 months	Very low
Matsumoto et al. [10]	0	1 (100) (after 2 recurrences, followed by drainage)	0	NBCA	NA	100	0	0	NA	Very low
Link et al. [29]	0	0	6 (100) (after 1 recurrence)	PVA	Significant reduction/ complete reduction	83	0	1 (17) (1 pt required surgical reevacuation)	15 weeks	Very low
Ban et al. [12]	27 (38)	45 (63) (followed by adjunctive hematoma removal)	0	PVA	SDH < 10 mm, no surgical rescue	98.6	0	1 (1.4) (1 pt required hematoma evacuation after additional head trauma)	6 months	Moderate
Link et al. [11]	32 (65)	0	17 (35) (10 as prophylaxis & 7 as a treatment, following drainage)	PVA	Reduction > 50%	68.9[4]	0	4 (89) (4 pts required surgical evacuation)	> 6 weeks	Moderate
Total	**64 (34)**	**63 (33)**	**63 (33)**	–	–	**96.8**	**3.6**	**10 (5)**	**6 months**	

underwent two previous surgical drainages and an MMAE; however, considering the multiple interventions, it was not clear if this it was a surgical or an MMAE complication [23].

Theoretical potential complications include transient facial nerve palsy and monocular blindness; however, these complications were not reported in the reviewed articles. As discussed by Link et al. [2], the petrosal branch of the MMA can supply the vasa nervous of the facial nerve and if this branch is seen on the angiogram, the interventionalist should advance the tip of the microcatheter past the origin of this branch in order to avoid reflux and potential complications. Evaluation of potential MMA branches that can form collaterals with the ophthalmic artery must also be sought. Of note, the orbital/meningolacrimal branch can potentially form anastomoses with the ophthalmic artery and, again, the microcatheter tip should be advanced distally to this in order to avoid reflux and embolization of ophthalmic branch collaterals [2].

3.4. Radiological & clinical outcome

The definition of cSDH resolution was not systematically reported and varied greatly between studies. The definitions ranged from no enlargement on follow up CT, volumetric reduction, significant reduction and all the way to complete resolution (see Table 3). Using these heterogeneous definitions, cSDH resolution was reported in 96.8% of cases. Ten patients (5.3%) suffered from cSDH recurrence after MMAE, and nine of them (4.7%) required unplanned surgical drainage while one patient's cSDH spontaneously regressed with time. The decision to intervene surgically after MMAE in these 9 cases was due to an absence of regression of the cSDH on follow-up CT imaging, residual symptoms following MMAE, a case of a secondary traumatic event months after MMAE, the case of subdural empyema previously mentioned, and lastly, an interesting case of bilateral cSDH [28]. This patient had bilateral cSDH and underwent bilateral craniotomies, which was followed by bilateral MMA embolization after bilateral recurrence was detected. On follow-up CT, there was an increase in size of the left cSDH and a slight decrease in the right cSDH, which was managed with surgical re-evacuation. On angiography, most of the hemorrhage was within the territory which correlated with a region supplied by a fascine meningeal branch artery arising from the left ophthalmic artery which supplied the anterior portion of the dura. This branch could not have been safely catheterized and embolized. As hypothesized by the authors, it is possible that the reason for treatment failure in this case was due to the large portion of the cSDH that was supplied by branches which could not be embolized, and therefore not due to the failure of the embolization itself [28].

Three studies that totaled 64 patients underwent MMAE as a primary sole intervention. Five patients in the Link et al. case series [1] had a 100% resolution rate and required no unplanned surgical intervention. In the Ban et al. [12], 27 patients underwent primary MMAE and 45 patients underwent MMAE followed by adjunctive surgical cSDH removal. The recurrence rates and the need for further surgical intervention was not specified between these two groups of patients; however, only one patient required unplanned surgical evacuation and this was following additional head trauma. Lastly, in the latest Link et al. case series [11], 32 patients underwent primary sole MMAE and 17 patients underwent MMAE after surgical drainage. Again, the recurrence rates and the need for further surgical intervention was not distinguished based on these subgroups. Four patients required further unplanned surgical intervention. Further investigation of the 4 cases by the authors failed to show any similarities between the cases that could be used as potential predictors of failure.

4. Discussion

The cSDH population is elderly and frail. Given the 11–37% [1–3] recurrence rate reported after surgical cSDH evacuation, the development of minimally invasive alternatives to surgery could be valuable. The treatment options for cSDH have been extensively studied and debated. The success of conservative management is low (ranging from 3 to 18%) [29,30]. Several medical options have been investigated, such as angiotensin-converting enzyme (ACE) inhibitors [31], statins [32], and corticosteroids [33]; however, these studies had negative results, low quality evidence, and increased adverse events, respectively. Anti-fibrinolytic medications [9,30] and corticosteroids [34], as well as continuing antiplatelet therapy [35] are currently the subject of prospective trials. Surgical drainage is considered the mainstay treatment for cSDH, and varying techniques such as burrhole versus craniotomy [36], number of burrholes [36], irrigation versus no irrigation [37,38], drain versus no drain [39,40], and drain localization have been studied [37,41,42]; however, the optimal surgical management remains the source of significant ongoing studies. Based on the pathophysiology of cSDH, MMAE could be an interesting paradigm. The current model of SDH chronicization involves the formation of an inflammatory membrane lining the dura mater capable of both perpetuating the hematoma and of bleeding acutely [43–45]. The generation of such a membrane involves neovascularization, in which the vessels are derived from the dura mater and perfused mainly by distal branches of the MMA [8]. Interruption of blood flow from the MMA to the dura, and thus the cSDH membrane, seems to be a reasonable approach to the treatment of cSDH. However, the safety and effectiveness of this treatment modality remains to be demonstrated.

In this systematic review, we identified only two prospective studies, of which one was uncontrolled and the other of which used historical controls. All other reports consisted of retrospective case series that did not systematically collect and report MMAE complications or the management of antithrombotic medications. The cSDH resolution definition ranged from no enlargement, volumetric reduction, significant reduction to complete resolution. When grouping these heterogeneous definitions together, successful management of cSDH with MMAE was achieved in 96.8% of reported cases. The lack of specificity regarding the definition of "cSDH resolution" is an important factor to highlight. More specifically, including definitions such as "no enlargement" in the positive resolution category creates a blending effect and introduces important bias. Furthermore, MMAE was frequently used as an adjunct treatment along with surgical drainage. This makes it difficult to realistically determine the effect of MMAE, as it is impossible to know how patients would have evolved with a surgical approach alone. The specific indications of MMAE are to be determined. The level of evidence of all papers was graded "very low", except for 3 that were considered "low" (Table 3). Hence, the level of evidence supporting MMAE is currently too low to recommend this procedure in routine clinical practice. What these reports demonstrate, however, is that MMAE is feasible in the cSDH population.

With regards to safety, no mortality from either the embolization nor the surgical treatment of cSDH was reported in any of the reviewed articles. Moreover, the complication rate related directly to the MMAE was of 3.6%. Given that the one-year mortality rate of cSDH reported in other studies is up to 69% in dependent patients [46] and that diagnostic angiography procedures have a well-documented complication rate of 0–2.6%, the accuracy of the safety assessment performed in the reviewed studies is doubtful [47,48]. The low rates of morbidity/mortality could be due to the short length of available follow-up, which totaled a median of 6 months, poor documentation of complications in the charts or due to selection bias. There is a high chance that the selected patients who underwent MMAE were not representative of the overall SDH population, due to inherent factors related either to their clinical presentation or their comorbidities. Patient characteristics, along with their comorbidities, were not systematically reported nor were they analyzed as an independent predictor of outcomes, mostly due to limited number of patients in each series. Therefore, the real morbidity of MMAE is probably much higher than reported here.

Together, we believe that this data supports the need, rationale and

feasibility of a formal randomized controlled trial of MMAE for cSDH. We are currently working on the lead-in phase of the Embolization of the Middle Meningeal Artery in Chronic Subdural hematoma (EMMACS) trial which will assess the safety and efficacy of MMAE in the anticoagulated cSDH population [study protocol submitted to ethics committee, [30]. As various groups gain and publish experience with this new paradigm, a role for MMAE in the management of cSDH may very well emerge.

5. Conclusion

MMAE is a feasible intervention in the cSDH population, although no conclusion can be reached concerning its safety or efficacy. Eighteen articles, graded "very low" to "low", involving 190 patients, have been published to date; therefore, the level of evidence supporting MMAE is currently too low to routinely recommend this procedure in clinical practice. Formal prospective, randomized, controlled trials are required before MMAE can be introduced into routine clinical practice.

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