



## Review Article

# Middle meningeal artery embolization for chronic subdural hematomas. A systematic review of the literature focused on indications, technical aspects, and future possible perspectives

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## ABSTRACT

**Background:** Chronic subdural hematoma (CSDH) is one of the most common neurosurgical diseases that affect elderly and fragile patients and as a consequence, management can be challenging. Surgery represents the standard treatment; however, alternative options are under investigation. Middle meningeal artery (MMA) embolization is considered a minimally invasive treatment although with poor evidence. In this review, we tried to summarize the findings about MMA embolization as a treatment for a CSDH to provide a useful guidance for clinical practice and for future speculative aspects.

**Methods:** Literature review on PubMed until March 2021 was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. We conducted a research on PubMed with a various combinations of the keywords "CSDH" and "middle meningeal artery" and "embolization," "refractory subdural hematoma," and then we reviewed the references of the relevant studies as additional source of eligible articles.

**Results:** Among the 35 studies eligible for this review, 22 were case series, 11 were case reports, one was a technical note, and 1 was a randomized trial. A total of 746 patients were found in the literature. Failure rate of MMA embolization was between 3.9 and 8.9% of the cases according the indication to treat CSDH (upfront vs. after surgery).

**Conclusion:** The global impression deriving from the data available and the literature is that MMA embolization is a safe procedure with very low complications and with a low failure rate, both when associated with surgery or in case of a standalone treatment.

**Keywords:** Chronic subdural hematoma, Middle meningeal artery embolization, Recurrent chronic subdural hematoma, Refractory subdural hematoma

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## INTRODUCTION

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical diseases characterized by the presence of an abnormal fluid collection in the subdural space made of blood and blood degradation compounds.<sup>[12]</sup> CSDH develops as a separation of dural border cells layer that triggers a healing inflammatory response. In this setting, the inflammatory chain is associated with the release of angiogenic cytokines. This reaction determines the development of a capillary network vascularized by the middle meningeal arteries (MMAs) which provide the blood flow to the dura mater.<sup>[12,23,49,53]</sup>

The overall incidence of CSDH ranges from 1.72 to 127.1/100.000 inhabitants, depending on the reports published in the literature, and it increases with age with the higher peak in patients over 65 years of age.<sup>[30,38]</sup>

For a subgroup of patients, a conservative approach may be proposed as first choice of treatment, but specific inclusion criteria for this “wait and see” management is far away to be clearly reported in literature.

Moreover, a conservative management, when indicated, is necessarily associated to a prolonged neuroradiological and clinical follow-up.<sup>[39,55]</sup>

In case of symptomatic CSDH, the standard treatment of care is mainly represented by surgical evacuation with several technical options described.<sup>[30,49]</sup> Nevertheless, surgical management is often challenging since it is associated with a high recurrence rate, morbidity and mortality,<sup>[2,6,8,11,29,40,49,53]</sup> especially when patients may present with many age related comorbidities that can affect the postoperative outcome.<sup>[8,29,49]</sup> An extreme variability is related to the clinical course after surgery such as postoperative/in hospital mortality reported

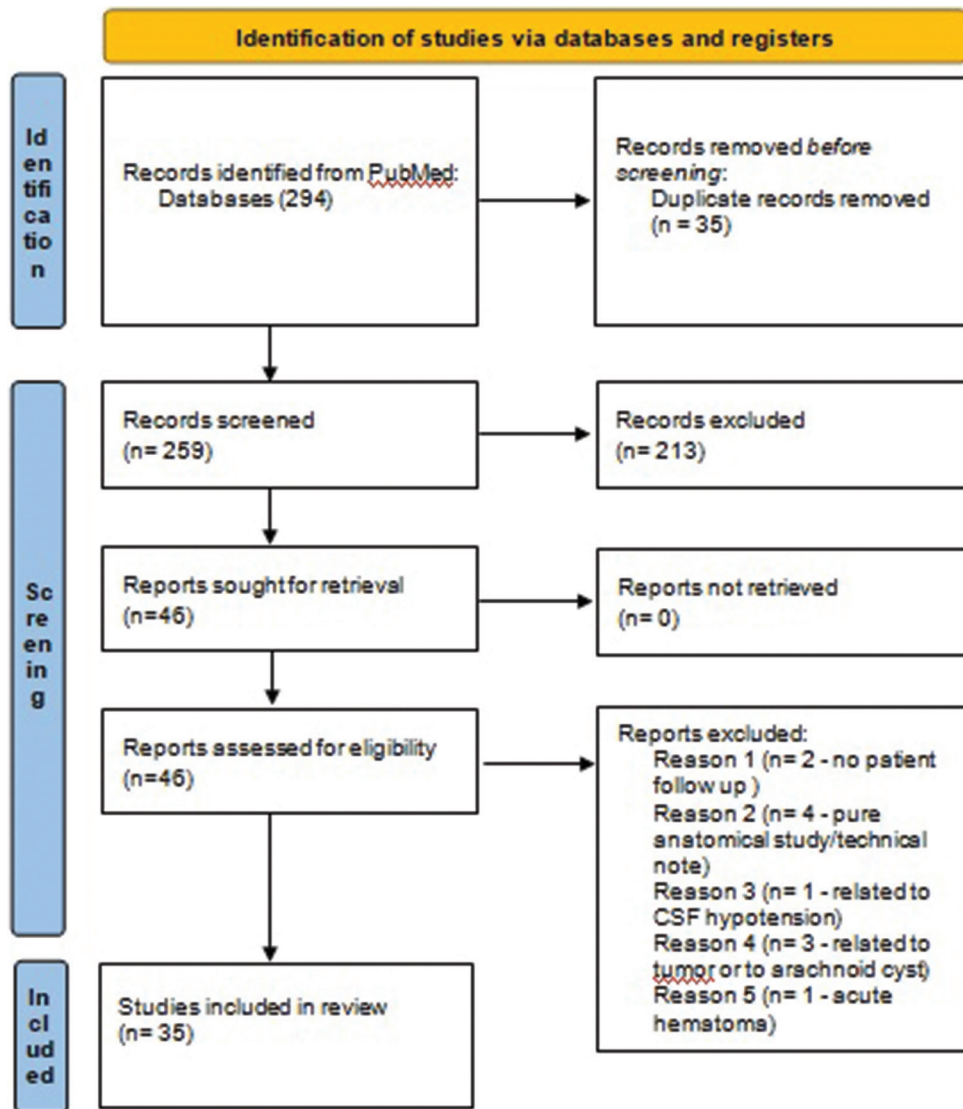


Figure 1: The PRISMA flow chart of our systematic review

from 2.3% to 27.5% and recurrence rates considered to be from 10% to 30% that may be connected to different prognostic factors such as age, comorbidities and use of anticoagulant or antiplatelet medications.<sup>[1,2,8,29,40,49,53]</sup>

The primary end-point of the surgical evacuation of CSDH is to release the intracranial hypertension and reduce the local mass effect.<sup>[12,53]</sup> Therefore, surgery is not meant to deal with the causes that lead to the CSDH formation, and this may justify the high failure rate.

As a consequence, starting from the pathophysiology of CSDH, several pharmacological approaches have been proposed to avoid surgery, when possible, like use of corticosteroids, tranexamic acid, or ACE-inhibitors<sup>[16,39,55]</sup> without a clear evidence.

More recently, in addition to those strategies, an interventional approach under investigation is the devascularization of the external membrane of the CSDH through the embolization of the MMAs.<sup>[7,23,27,44,45]</sup> At present, the literature data seem more prone to suggest this endovascular treatment for recurrent CSDH and/or for hematoma with no clear surgical indication.

The aim of our work is to provide an updated review about the findings regarding the efficacy of MMA embolization in CSDH with particular focus on open questions regarding this new technique:

1. When to propose MMA embolization as a standalone treatment.
2. The efficacy of MMA embolization in preventing CSDH recurrences after surgical drainage.
3. Possible criteria for selecting patients for MMA embolization.

## MATERIALS AND METHODS

### Literature review

We reviewed the existing literature on PubMed until March 22, 2021, in English language, without restrictions about the paper publication status, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.<sup>[31]</sup> We conducted research on PubMed with a various combinations of the keywords “CSDH” and “middle meningeal artery” and “embolization” and “refractory subdural hematoma.” Then we reviewed the references of the relevant studies as additional source of eligible articles. We decided to include works specifically focused only on CSDH and treatment with MMA embolization without limitation about the kind of work and to exclude pure reviews (without new cases) and editorials.

Afterward, all titles and abstracts were screened to exclude unrelated studies; this includes neurological conditions other than/causing other than CSDH (e.g., acute subdural

hematomas, epidural hematomas, and tumor related CSDHs), studies about anatomy of MMA, studies without patients’ follow-up (either clinical or radiological) and spinal hematomas. Some other studies could have successively been excluded after full-text article reading.

Data of the eligible works were obtained through careful analysis of full text by one author and checked by another.

After having analyzed all the methods of the studies, patients were also classified according to indication for MMA embolization into the following:

1. Standalone embolization.
2. Symptomatic CSDH (close to surgery to prevent recurrence or as prophylaxis for a recurrence).
3. Recurrent CSDH.
4. Recurrent after second surgery.

Case series with more than four patients and including a comparison with a control group were selected for further analyses and for comparison with our series of patients.

## RESULTS

Throughout literature searching on PubMed (MEDLINE) 340 articles were reported with several combinations of the keywords described in the “methods” section. Four articles were eligible for reviewing after reference check. As a consequence, a total of 344 articles were screened for the review. Three-hundred and nine articles were excluded on the basis of the inclusion criteria of the present review [Figure 1].

For each study, we extrapolated the indication for MMA embolization, the number of patients treated, the kind of study, the kind of surgery, the number of MMAs embolized, the number of treatment failures, the presence or absence of a control group, and the number of complications related to MMA embolization. All results are summarized in [Table 1].

### General considerations

Among the 35 studies eligible for this review, 22 were case series, 11 were case reports, one was a technical note, and one was a randomized trial. Among the 22 case series, five presented comparisons with an historical group of patients treated in a conventional way.

Starting from year 2000 with the first report by Mandai *et al.*<sup>[25]</sup> till 2018, a total of 13 works could be considered eligible for analysis in this review while an increase of publications has been observed starting from 2019 with 22 works published in the past 27 months.

A total of 746 patients have been described in literature till the date of the literature search. According to the published papers, we divided the studies reported in the literature into two groups; those that proposed MMA embolization only

Table 1: Cases reported in the literature.

S. No.	Author	Year	Kind of article	Number of pts	Rt	Lf	Bil	Number of patients according indication for treatment			Kind of surgery	MMA embolization			Conclusions			
								Upfront CSDH (close to surgery to prevent recurrence)	Symptomatic CSDH	Recurrent CSDH (after second surgery)		Rt	Lf	Bil		Num-ber of failures	Aborted procedures	Procedure related complications
1.	Shinya Mandai <i>et al.</i>	2000	Case report	1	1	0	0	0	0	0	1	Burr hole	1	0	0	0	None	Prevention of recurrence in a patient with multiple recurrences
2.	Hirai <i>et al.</i>	2004	Case report	2	1	0	1	0	0	2	0	Burr hole	1	0	1	0	0	Prevention of recurrence in two patients on oral antico- agulant
3.	Masaki Mino <i>et al.</i>	2010	Case series	4	1	1	2	0	0	3	1	Burr hole/ craniotomy	1	1	2	0	0	MMA embolization can be effective adjuvant procedure to prevent or delay the recurrence
4.	Takao Hashimoto <i>et al.</i>	2013	Case series	5	1	3	1	0	0	2	3	n.r.	1	3	1	0	0	MMA embolization is effective to prevent recurrence of CSDH with low complication rates
5.	Hideo Chihara <i>et al.</i>	2014	Case report	1	0	1	0	0	0	0	1	Burr hole	0	1	0	1	0	MMA embolization failed to prevent recurrence.
6.	Akira Tempaku	2015	Case series	5	2	1	2	0	0	0	5	Burr hole	2	1	2	0	0	Possible collateral networks? MMA embolization performed
7.	Kim	2017	Case series	20	n.r.	n.r.	6	0	0	20	0	Burr hole	n.r.	n.r.	6	0	0	performed in 4/5 cases. No recurrences after MMA embolization +/- surgery
8.	Matsumoto <i>et al.</i>	2017	Case series	4	n.r.	n.r.	n.r.	0	0	0	4	Burr hole	n.r.	n.r.	n.r.	0	0	MMA embolization alone at CSDH recurrence
9.	Link <i>et al.</i>	2017	Case series	5	0	3	2	5	0	0	0	none	0	3	2	0	0	After second recurrence, MMA embolization + irrigation is not different to irrigation alone

(Contd...)

Table 1: (Continued).

S. No.	Author	Year	Kind of article	Number of pts	Rt	Lf	Bil	Number of patients according indication for treatment			Kind of surgery	MMA embolization			Conclusions				
								Upfront CSDH (close to surgery to prevent recurrence)	Symptomatic CSDH	Recurrent CSDH (after second surgery)		Rt	Lf	Bil		Num-ber of failures	Aborted procedures	Procedure related complications	
10.	Sirh <i>et al.</i>	2018	Case report	1	0	1	0	0	0	1	0	Burr hole	0	0	0	None	Case report. Prevention of recurrence in a patient with CSDH related leukemia MMA embolization facilitates resolution and prevents reaccumulation of CSDH and is more effective than convention treatment.		
11.	Ban <i>et al.</i>	2018	Case series	72	25	28	19	27	45	0	0	Burr Hole/ Craniotomy	25	28	19	1	0	None	MMA embolization facilitates resolution and prevents reaccumulation of CSDH and is more effective than convention treatment.
12.	Link <i>et al.</i>	2018	Case series	49	24	14	11	32	10	7	0	Burr Hole/ Craniotomy	24	14	11	4	0	None	MMA embolization may represent an alternative to surgery for new or recurrent chronic SDH, or as prophylaxis to reduce the risk of recurrence after surgery.
13.	Link <i>et al.</i>	2018	Case series	6	1	4	1	0	0	6	0	Craniotomy	1	4	1	1	0	None	MMA embolization may represent an effective alternative to surgery
14.	Okuma <i>et al.</i>	2019	Case series	17	5	8	4	0	17	0	0	Burr hole	5	8	4	0	0	None	MMA embolization was not associated with recurrent CSDH or rehospitalization in our department in the current case series
15.	Entezami <i>et al.</i>	2019	Case report	2	0	2	0	1	1	0	0	Burr hole	0	1	0	0	0	None	Embolization was not associated with recurrent CSDH
16.	Entezami <i>et al.</i>	2019	Case report	1	1	0	0	1	0	0	0	n.r.	0	0	0	0	0	None	MMA embolization feasible for CSDH treatment

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Table 1: (Continued).

S. No.	Author	Year	Kind of article	Number of patients			Number of patients according indication for treatment				Kind of surgery	MMA embolization				Conclusions		
				Rt	Lf	Bil	Upfront CSDH (close to surgery to prevent recurrence)	Symptomatic CSDH	Recurrent CSDH (after second surgery)	Rt		Lf	Bil	Num-ber of failures	Aborted procedures		Procedure related complications	
17.	Nakagawa <i>et al.</i>	2019	Case series	20	n.r.	8	0	0	0	20	Burr hole	n.r.	n.r.	8	0	0	None	rehospitalization in our department in the current case
18.	Waqas <i>et al.</i>	2019	Case series	8	1	6	1	6	0	2	n.r.	1	6	1	0	0	None	MMA can be useful for cases of recurrent CSDH in which anticoagulation or antiplatelet therapy is strongly indicated
19.	Wang <i>et al.</i>	2019	Case report	2	0	0	2	1	1	0	Burr hole	1	1	0	1	0	None	MMA failed to prevent evolution of a small CSDH
20.	Piergallini <i>et al.</i>	2019	Case report	2	0	1	1	0	2	0	n.r.	0	1	1	0	0	None	Development of AV fistula after MMA embolization
21.	Kan <i>et al.</i>	2020	Case series	138	54	70	15	93	0	45	Burr hole/ Craniotomy	69	85	15	9	0	2	MMA embolization may provide a safe and efficacious minimally invasive alternative to conventional surgical techniques
22.	Eimad Shohar <i>et al.</i>	2020	Case series	89	n.r.	n.r.	15	0	89	0	Burr hole	0	15	4	8	8	None	MMA reduces the risk of recurrence when compared to historical cohort
23.	Rajah <i>et al.</i>	2020	Technical note	1	0	1	0	1	0	0	none	0	1	0	0	0	None	MMA via radial artery with onyx DynaCT after embolization demonstrates a vascular network supplying CSDH
24.	Mureb <i>et al.</i>	2020	Case series	8	5	3	0	n.r.	n.r.	n.r.	n.r.	5	3	0	0	0	None	Perioperative embolization of MMA is safe and effective
25.	Arham <i>et al.</i>	2020	Case report	1	0	1	0	0	1	0	Burr hole	0	1	0	0	0	None	

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Table 1: (Continued).

S. No.	Author	Year	Kind of article	Number of pts	Rt	Lf	Bil	Number of patients according indication for treatment			Kind of surgery	MMA embolization				Conclusions		
								Upfront CSDH (close to surgery to prevent recurrence)	Symptomatic CSDH (after second surgery)	Recurrent CSDH		Rt	Lf	Bil	Num-ber of failures		Aborted procedures	Procedure related complications
26.	Yokoya <i>et al.</i>	2020	Case report	2	1	1	0	0	0	0	0	0	0	0	0	None	Benefit of MMA after re-current CSDH treated with craniotomy	
27	Yajima <i>et al.</i>	2020	Case series	18	n.r	n.r	n.r	3	n.r	n.r	n.r	0	0	0	0	None	Benefit of MMA embolization in preventing CSDH recurrence	
28.	Shotar <i>et al.</i>	2020	Case report	1	0	0	1	0	0	0	Burr hole	0	1	1	0	None	Development of an AV fistula 3 months after MMA embolization	
29.	Gomez-Paz <i>et al.</i>	2020	Case series	23	n.r	18	n.r	23	0	0	n.r.	0	0	3	0	None	MMA alone in patients with or without midline shift but few symptoms can resolve CSDH	
30.	Catapano <i>et al.</i>	2020	Case series	35	n.r	n.r	n.r	20	8	9	n.r.	16	13	6	1	0	1	MMA embolization of CSDHs appears to be both safe and efficacious. Furthermore, embolization of both the anterior and posterior MMA branches may be associated with increased odds of complete resolution
31.	Joyce <i>et al.</i>	2020	Case series	121	n.r	n.r	n.r	51	17	53	Burr hole/craniotomy	69	52	30	9	3	3	MMA embolization can be used safely and effectively as stand alone or as adjunctive treatment
32.	Ng <i>et al.</i>	2020	Clinical trial	21	n.r	n.r	4	0	21	0	Burr hole/craniotomy	n.r	n.r	n.r	1	1	None	MMA embolization in addition with surgery reduces the time needed for resorption of the hematoma

(Contd...)



Table 1: (Continued).

S. No.	Author	Year	Kind of article	Number of pts	Rt	Lf	Bil	Number of patients according indication for treatment			Kind of surgery	MMA embolization			Conclusions				
								Upfront CSDH (close to surgery to prevent recurrence)	Recurrent CSDH	Recurrent CSDH (after second surgery)		Rt	Lf	Bil		Num-ber of failures	Aborted procedures	Procedure related complications	
33.	Rajah <i>et al.</i>	2020	Case series	46	21	19	6	37	4	5	0	Burr hole	21	19	6	5	2	None	MMA is safe and effective
34.	Entezami <i>et al.</i>	2021	Case series	5	3	1	1	4	0	1	0	Burr hole	3	1	1	0	0	None	MMA embolization alone may be of benefit in the management of CSDH in an outpatient setting
35.	Tiwari <i>et al.</i>	2021	Case series	10	n.r.	n.r.	3	4	0	6	0	n.r.	n.r.	n.r.	3	0	0	None	MMA embolization contributed to a marked reduction in SDH volume postoperatively
Total				746	147	187	106	309	217	164	35		247	248	137	41	14	6	

Rt: Right; Lf: Left; Bil: Bilateral; Upfront: Upfront embolization/standalone embolization. CSDH: Chronic subdural hematoma, MMA: Middle meningeal artery

as a first treatment for a CSDH and those that proposed MMA embolization as an adjunctive treatment after surgical drainage. The last group included patients that underwent MMA embolization as prophylaxis for recurrence, patients that were treated with MMA embolization in case of CSDH recurrence and patients that underwent MMA embolization as a salvage option in case of multiple recurrences. This kind of subdivision is reported in [Table 1].

### MMA embolization alone for CSDH

MMA embolization was reported as a standalone treatment for a CSDH in 16/35 works and of these 16 studies, four were case reports. In these 16 works about standalone MMA embolization for CSDH treatment, a total of 309 patients (41.4% of total reported patients) were studied but some of them received a MMA embolization as a standalone treatment of a recurrent CSDH.

Indication for MMA embolization alone was different from one study to another [Table 2]. In some cases, MMA embolization was performed as per patients' preferences.<sup>[13]</sup> In the majority of the patients reported in the works by Link and Ban, MMA embolization alone was performed after failure of a conservative management for mildly symptomatic patients.<sup>[7,23]</sup> In four studies, MMA embolization was proposed in patients under anticoagulant or antiplatelets treatments in order to prevent risk of subdural collection enlargement or to avoid suspension of such medications.<sup>[13,18,35,52]</sup> In particular, in 2021, Entezami *et al.* proposed MMA embolization as an alternative therapy for the management of CSDHs as a day case procedure in the COVID pandemic scenario.<sup>[13]</sup> Two works did not report the criteria used for selecting patients eligible for MMA embolization but just reported the outcome (e.g. Joyce *et al.* 2020 or Mureb *et al.* 2020) or included patients with different indications.<sup>[19,32]</sup>

Surgical rescue or refilling of subdural collection was considered the criteria for the failure of MMA embolization in all papers. In case MMA embolization was performed as a standalone treatment, the failure rate was 8.9% (8 patients out of 90); while the remaining patients experienced in all cases a resolution of the subdural collection at the follow-up CT scans. This failure rate was calculated taking into account only those studies in which it was possible to correlate treatment failure and indication to treat with MMA embolization alone. In some studies, like the one by Catapano *et al.*, it is not specified who failed treatment with MMA embolization (patients treated for asymptomatic CSDHs with MMA embolization alone or patients treated for a recurrent CSDH after surgery?<sup>[9]</sup>)

A comparison series of patients undergoing conventional treatment is reported only by Ban *et al.* in which no failure was associated with MMA embolization for these kinds of patients.<sup>[7]</sup>



**Table 2:** Summary of indications for case series for upfront treatment of CSDH with MMA embolization.

MMA alone	Year	Kind of paper	Number of pts	Criteria
Thomas Link	2017	Case series	5	Failed conservative management in patients with mild hematomas
Seung Pil Ban	2018	Case series	27	Asymptomatic patients
Thomas Link	2018	Case series	32	Failed conservative management in patients with mild hematomas
Pouya Entezami	2019	Case report	1	Patient's preference
Pouya Entezami	2019	Case report	1	fragile elderly patient
Waquas	2019	Case series	6	Pts under anticoagulation or antiplatelets
Henglu Wang	2019	Case report	1	Prevention of enlargement
Gary B. Rajah	2020	Technical note	1	Patient's preference
Hirohisa Yajima	2020	Case series	3	Patients at high risk for recurrence
Santiago Gomez-Paz	2020	Case series	23	n.r.
Joshua Catapano	2020	Case series	20	n.r.
Gary B. Rajah	2020	Case series	37	Patients mildly symptomatic and CSDH larger than 5 mm. No focal deficits. No midline shift.
Peter Kan	2020	Case series	93	Case by case decision. Symptomatic CSDH with midline shift
Evan Joyce	2020	Case series	51	n.r.
Gary B. Rajah	2020	Case series	37	Any patient with subacute/chronic SDH larger than 5mm
Pouya Entezami	2021	Case series	4	Patient's on anticoagulants/outpatient's management in COVID pandemic
Ambooj Tiwari	2021	Case series	4	Subacute or chronic hematomas

CSDH: Chronic subdural hematoma, MMA: Middle meningeal artery

### MMA embolization after surgery for the prevention of CSDH recurrence or as a salvage treatment for recurrent CSDH

In 14/35 (40%) studies, MMA embolization was proposed as a prophylactic treatment to prevent recurrence and in 5 of them, indication for treatment overlapped between standalone treatment, prophylactic treatment and treatment at recurrence. Four works were case reports. These studies included a total of 305 patients (41.4% of total reported patients). One study did not report the number of patients treated in a prophylactic way making some of the results partly uncompleted.<sup>[52]</sup>

In general, patients were eligible for MMA embolization when they were considered high risk for CSDH recurrence but the way it was assessed differed among the studies. Okuma *et al.* in 2019 established a checklist for high risk CSDHs that were used to select patients at high risk and patients at low risk for recurrence.<sup>[35]</sup> In the study by Ban *et al.*, 45 consecutive patients were enrolled and treated with CSDH surgical drainage and MMA embolization without any selection criteria for MMA embolization.<sup>[7]</sup> In the series of 60 patients described by Link in 2018, 17 patients were treated after surgical evacuation of a CSDH. In their work they treated consecutively such patients but they did not report the motivations that lead to propose MMA embolization as prophylaxis.<sup>[23]</sup> In the study by Shotar *et al.*, MMA embolization was proposed as prophylaxis in those patients with at least one known risk factor for recurrence but this decision was under the personal experience of the medical

staff involved in the treatment of a patient.<sup>[41]</sup> In the study by Joyce *et al.* in 2020, they reviewed a multi-institutional database but they did not specify the selection criteria for MMA embolization.<sup>[19]</sup> In patients enrolled in the clinical trial by Ng and colleagues, the randomization after surgery was the only criteria for MMA embolization after surgery and this is the only experience of this kind reported in literature.<sup>[34]</sup>

In 14/35 studies MMA embolization was proposed as an alternative treatment after surgery for recurrent CSDH to prevent a second surgery. Patients included in this group were 158 accounting for 21.2% of the total cases described in literature. Three of the studies in this group were case reports.

In 8/34 studies, MMA embolization was proposed as a salvage treatment after second recurrence. The majority of the publications in this group were produced between the years 2000 and 2015; year after which the number of patients included in case series increased. In this scenario MMA embolization was performed on 35 patients (4.6% of the total number of patients) of which 18/35 were described between the year 2000 and the year 2015.

### Failure rates of MMA embolization and procedural complications

Analyzing the 746 patients reported in the literature, 41 patients reported a failure of MMA embolization to prevent

surgery or hematoma refilling with an overall failure rate of 5.5% while considering the series with more than 20 patients included, the failure rate remained quite the same at 5.6% with 28 patients on a total of 496 reported in 11 works [Table 3]. In all the studies considered with more than 20 patients, MMA embolization was proposed with all the four indications but only one study enrolled patients with more than one CSDH recurrence.<sup>[31]</sup> The majority of patients treated with MMA embolization were described in publications from year 2017; while before that year, the number of patients in case series was smaller. Considering the single indication to perform MMA embolization, the failure rate was different from one group to another. In studies dealing with MMA embolization with multiple indications, it was difficult to define which patients failed to respond to MMA embolization according to the indication. So far, in the following considerations, we included only those cases in which it was possible to determine the nature of the indication.

As reported above, failure rate after MMA embolization alone was 8.9% while in case of MMA performed as a recurrence prophylaxis after surgery, the failure rate was 3.9% (six patients out of 195). In case of MMA embolization performed after CSDH recurrence it was not possible to measure the failure rate since only the study by Link in 2018 was described a failure on a series of 6 patients;<sup>[24]</sup> while in other studies with overlapping indications for MMA embolization, it was not specified the number of failures after MMA embolization. Finally, in case of MMA embolization performed after second recurrence, failure rate was 2.9% (1 patient out of 35).

Complications of MMA embolization was reported in six cases with a consequent very low rate with a global rate of 0.8% on 746 patients. Treatment failure was considered as a separate complication. Complications encompassed one cerebral infarction, one seizure, one intermittent aphasia, one cerebrovascular complication, one cerebrovascular infarction, and one acute worsening of CSDH.

### Studies including a comparison group with conventional treatment

In the literature, five studies encompassed a comparison group. In five studies a comparison group made by an historical cohort of patients treated with conventional technique.

In total, the control groups of the five studies included 727 patients whose outcome was compared with 205 patients undergoing MMA embolization with heterogeneous indications.

Globally, patients that received MMA embolization showed a lower recurrence rate and required less surgical procedures. In fact, the failure rate of MMA embolization in preventing surgery was 3.9% (6 patients on 155) while the recurrence rate

after conventional treatment in historical cohorts was 29.5% (214 patients on 727 patients). Most of the patients were treated with MMA embolization for recurrent hematomas while only 27 patients enrolled in the work by Ban *et al.* were treated with MMA embolization alone with no cases of failure.<sup>[7]</sup>

## DISCUSSION

### Considerations about indications for MMA embolization

From the analysis of the literature, we identified four indications for MMA embolization:

- To prevent surgery in patients with paucisymptomatic CSDHs,<sup>[7,9,13-15,19,20,24,35-37,48,50,51]</sup>
- As prophylaxis of a recurrence after a first surgery,<sup>[5,7,9,14,19,24,34-37,41,42,50]</sup>
- After a first recurrence to prevent further recurrence,<sup>[9,13,17-21,23,24,28,37,43,48,51,54]</sup>
- As an adjunctive treatment in case of a second surgery.<sup>[10,17,25,26,28,33,47]</sup>

The first scenario is completely different; after standalone MMA embolization the remaining subdural fluid collection may be at risk of progression due to its pro-inflammatory features. In the other scenarios with the combined treatment, surgical evacuation can decrease the pro-inflammatory and vasogenic content of the subdural fluid collection, while the vascularization of the parietal membrane of the CSDH itself is reduced by MMA embolization.<sup>[12,22,46]</sup>

Thus, this pathophysiological difference may be related to the lower failure rate observed in CSDHs treated with combined procedures respect to the first scenario (3.9% vs. about 8.9%).

Standalone MMA embolization has been successfully achieved in all 27 cases reported by Ban *et al.* in 2017;<sup>[7]</sup> while a failure rate of 16% has been reported by Catapano *et al.* in 2020 but it may be due to the fact that the inclusion criteria were also extended to patients with midline shift more than 5 mm that could be more prone to become symptomatic and to consequently require surgical evacuation.<sup>[9]</sup>

Finally, the high rate of successful MMA embolization after first surgical evacuation or after recurrence should take in consideration a fraction of patients who could still have recovered completely after surgery even without MMA embolization and the low risk of further recurrences.

In fact, among a series of 372 patients treated for a CSDH, only 20 cases (5.4%) experienced a third recurrence that underwent MMA embolization as reported by Waqas *et al.* in 2017.<sup>[51]</sup>

This is summarized in [Table 1] along with the literature how indication for MMA embolization has changed; being reported at the beginning as a salvage treatment<sup>[17,25,26,33,47]</sup> then as a treatment aimed at preventing recurrence, mainly for patients under anticoagulant or antiplatelet medications.<sup>[19-21,52]</sup>

**Table 3:** Summary of the case series including more than 20 patients.

Author	Year	Kind of article	Number of pts	Right	Left	Bilateral	Asymptomatic CSDH	Symptomatic CSDH (close to surgery to prevent recurrence)	Recurrent CSDH	Recurrent CSDH (after second surgery)	Kind of surgery	Right	Left	Bilateral	Nuber of failures	Aborted embolizations	Procedure related complications
Kim <i>et al.</i>	2017	Case series	20	n.r.	n.r.	6	0	0	20	0	Burr hole	n.r.	n.r.	6	0	0	None
Link <i>et al.</i>	2018	Case series	49	24	14	11	32	10	7	0	Burr hole/ craniotomy	24	14	11	4	0	None
Ban <i>et al.</i>	2018	Case series	72	25	28	19	27	45	0	0	Burr hole/ craniotomy	25	28	19	1	0	None
Nakagawa <i>et al.</i>	2019	Case series	20	n.r.	n.r.	8	0	0	0	20	Burr hole	n.r.	n.r.	8	0	0	None
Ng <i>et al.</i>	2020	Clinical trial	21	n.r.	n.r.	4	0	21	0	0	Burr hole/ craniotomy	n.r.	n.r.	n.r.	1	1	None
Gomez-Paz <i>et al.</i>	2020	Case series	23	n.r.	18	n.r.	23	0	0	0	n.r.	0	0	0	3	0	None
Catapano <i>et al.</i>	2020	Case series	35	n.r.	n.r.	n.r.	20	8	9	n.r.	n.r.	16	13	6	1	0	1
Rajah <i>et al.</i>	2020	Case series	46	21	19	6	37	4	5	0	Burr hole	21	19	6	5	2	None
Shotar <i>et al.</i>	2020	Case series	89	n.r.	n.r.	15	0	89	0	0	Burr hole			15	4	8	None
Joyce <i>et al.</i>	2020	Case series	121	n.r.	n.r.	n.r.	51	17	53	0	Burr hole/ craniotomy	69	52	30	9	3	3
Kan <i>et al.</i>	2020	Case series	138	54	70	15	93	0	45	0	Burr hole/ craniotomy	69	85	15	9	0	2
Total			496	70	79	69	190	194	94	20		155	126	101	28	14	4

CSDH: Chronic subdural hematoma

At present, MMA embolization represents the first therapeutic option in the majority of cases reported in literature.<sup>[7,9,13,13-15,19,20,24,35-37,48,50,51]</sup> Nevertheless, the eligibility of patients is not yet well established, or even left to the surgeon's judgment as reported by Kan *et al.* in 2020,<sup>[20]</sup> or to patient's preference as reported by Entezami *et al.* in 2021.<sup>[13]</sup> Thus, the indication for a MMA embolization appears now to be more wide than strictly associated to the recurrence prevention although with such data collected in the context of different pathophysiological scenarios, is not correct to perform statistical comparisons among each group of patients.

### Number of MMA embolization, number of patients treated and outcome

The total amount of the number of patients that underwent MMA embolization is not well reported in literature. Some authors provide the number of CSDH treated but not the number of patients, such as in the series reported by Santiago Gomez-Paz *et al.* or by Joyce *et al.*,<sup>[15,19]</sup> where a bilateral blood collection is considered as 2 CSDH and not as one patient. Some authors reported indications that may overlap on the same patient so a bilateral hematoma could be operated just on one side but may be treated bilaterally with two different indications; one as upfront treatment and the other as a prophylactic treatment as reported, for example, by Sirh *et al.* in 2018.<sup>[43]</sup> So far, this way of taking into account bilateral subdural collections and analyzing data may not have a clinical utility since in daily practice, patients with bilateral CSDHs represent a single entity to deal with and maybe they should be considered as well in studies on MMA embolization with separate analyses or in separate papers from unilateral CSDHs. This consideration is also in line with some authors that consider patients with bilateral collections as different kinds of patients due to the increased risk for recurrence than patients with unilateral CSDH.<sup>[3,4]</sup>

In addition, the indication to proceed with the MMA embolization is not always well reported. Yajima *et al.* included patients with an objectively inclusion criteria as a third recurrence, and a more subjective inclusion criteria as the risk of recurrence without differentiating the results for each of these two groups.<sup>[52]</sup> Joyce *et al.* reported a big series of 151 embolization of MMA for CSHD. The indication for MMA embolization was not stated but they reviewed a multi-institutional database of patients in which were included both patients treated with standalone MMA embolization or after surgical evacuation.<sup>[19]</sup>

Moreover, in case of patients included for a standalone MMA embolization, there is no agreement about eligibility of candidates. While a poor symptom set seems to be generally reported as clinical inclusion criteria, conversely some neuroradiological data, like the midline shift, are considered exclusion criteria by Ban *et al.*<sup>[7,9]</sup> and inclusion criteria by Catapano *et al.*<sup>[9]</sup>

### Should we consider a standardized way for describing case series in view of future speculations?

The difficulty in systematically reviewing the data of the literature is the heterogeneity of data itself. The number of patients treated should be considered differently from the number of CSDHs treated and, in particular, bilateral CSDHs should be considered a category of patients separately due to their predisposition to develop a recurrent hematoma.

Patients should also be categorized by indication for MMA embolization given the different rate of procedure failure with regards to the indications for it and additionally the time between surgery and MMA embolization should be specified. This would allow to understand if there is a maximal length of time to perform a MMA embolization.

Moreover, patients under antiplatelet or anticoagulant medications could be considered for separate studies since they sometimes represent a clinical challenge (patients at risk for acute hemorrhages after surgery or at risk for complications related with drug discontinuation). In fact, contrary to what happens for surgical drainage, MMA embolization can be performed without suspending administration of pro-hemorrhagic drugs. Moreover, MMA embolization in addition to surgery may be of help in reducing the risk of CSDH recurrence and consequently, the complications related to discontinuation of anti-platelet or anticoagulant medications.

Although the great heterogeneity of the cases found in the literature, past experiences are of great importance in leading the neurosurgical community to trace a way to understand the efficacy and usefulness of invasive treatments. According to the experiences reported in literature, two points are of paramount importance in depicting future scenarios and they are related to the presence of the two main groups of patients with CSDH treated with MMA embolization; one group treated with standalone MMA embolization and the other treated after surgery.

First, from a pathophysiological point of view, the clear cut between these two groups is due to the presence of a residual CSDH collection that can reduce the efficacy of MMA embolization. Indirect evidence is related with the lower failure rate in case MMA embolization is performed soon after surgery. In this view, the neurosurgical community might look forward to better understand if some patients affected by a CSDH may have the opportunity to avoid a surgical drainage of the CSDH. A clear demonstration of such evidence would have a significant impact on social and economic costs since MMA embolization alone can be managed as a day-case procedure as proposed during the SARS-Cov2 pandemic.<sup>[13]</sup>

Second, performing MMA embolization after surgery may lead to reduction of CSDH recurrence rate and may reduce the timing needed for CSDH resolution leading to a possible



consequent reduction in in-hospital days, morbidity and mortality due to hospitalization. Finally, reduction in the number of surgeries required in case of recurrence may reduce the economic costs of the CSDH disease. Taken together, these considerations would lead to a global benefit to the community since CSDH incidence is expected to increase over the next years.<sup>[22,29,49]</sup>

Starting from these considerations, two kind of randomized clinical trials would be needed: one comparing conventional surgery versus standalone MMA embolization for poorly symptomatic subdural collections and one comparing conventional surgery versus surgery plus MMA embolization for CSDHs. In July 2020, Ng *et al.* published the first clinical trial on CSDH treatment with MMA embolization. They performed a randomized clinical trial allocating 21 patients for surgery alone and 25 patients for surgery + MMA embolization. They published a preliminary report of their trial demonstrating that MMA embolization after surgery reduces the time needed for CSDH absorption.<sup>[34]</sup> This study may represent a milestone in this field.

## CONCLUSION

In this review, we tried to summarize the findings about MMA embolization as a treatment for a CSDH in order to provide a useful guidance for the clinical practice and for future speculative aspects about alternative CSDH treatments. A significant limitation of our work is related with the lack of distinction in several works about the failure rates of MMA embolization according to the indication for which the treatment has been proposed. As a consequence, it is not possible to understand which patient failed to respond to MMA embolization (upfront treatment vs. postsurgical) and it is not possible to draw the exact number of patients but only the exact number of subdural collections that may affect the same patient or different patients. However, the global impression deriving from the data available and the literature is that in the near future, MMA embolization is a safe procedure with very low complications and with a low failure rate and will probably become one of the standards of care.

## Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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## Conflicts of interest

There are no conflicts of interest.

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