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 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 to 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
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.\(^\text{[12]}\) 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.\(^\text{[12,23,49,53]}\)

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.\(^\text{[30,38]}\)

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.

In case of symptomatic CSDH, the standard treatment of care is mainly represented by surgical evacuation with several technical options described.\(^\text{[30,49]}\) Nevertheless, surgical management is often challenging since it is associated with a high recurrence rate, morbidity and mortality,\(^\text{[2,6,8,11,29,40,49,53]}\) especially when patients may present with many age related comorbidities that can affect the postoperative outcome.\(^\text{[8,29,49]}\)

An extreme variability is related to the clinical course after surgery such as postoperative/in hospital mortality reported
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.\[1,2,8,29,40,49,53\]

The primary end-point of the surgical evacuation of CSDH is to release the intracranial hypertension and reduce the local mass effect.\[12,23\] 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\[16,19,55\] 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.\[7,23,27,44,45\] 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.\[31\] 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.\[25\] 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
| 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 Symptomatic CSDH (close to surgery to prevent recurrence) | Rt | Lf | Bil | Number of failures | Aborted procedures | Procedure related complications |
| 1.    | Shinya Mandai et al.  | 2000 | Case report     | 1             | 1  | 0  | 0   | 0 0 0 0 0 1 Burr hole                                  | 1 0 0 0 0 0 0   | None            | Prevention of recurrence in a patient with multiple recurrences |
| 2.    | Hirai et al.          | 2004 | Case report     | 2             | 1  | 0  | 1   | 0 0 2 0 Burr hole                                   | 1 0 1 0 0 0 0   | None            | Prevention of recurrence in two patients on oral anticoagulant |
| 3.    | Masaki Mino et al.    | 2010 | Case series     | 4             | 1  | 1  | 2   | 0 0 3 1 Burr hole/ craniotomy                         | 1 1 2 0 0 0 0   | None            | MMA embolization can be effective adjuvant procedure to prevent or delay the recurrence |
| 4.    | Takao Hashimoto et al.| 2013 | Case series     | 5             | 1  | 3  | 1   | 0 2 3 n.r.                                            | 1 3 1 0 0 0 0   | None            | MMA embolization is effective to prevent recurrence of CSDH with low complication rates |
| 5.    | Hideo Chihara et al.  | 2014 | Case report     | 1             | 0  | 1  | 0   | 0 0 1 Burr hole                                     | 0 1 0 1 0 0 0   | None            | MMA embolization failed to prevent recurrence. Possible collateral networks? |
| 6.    | Akira Tempaku         | 2015 | Case series     | 5             | 2  | 1  | 2   | 0 0 5 Burr hole                                     | 2 1 2 0 0 0 0   | None            | MMA embolization performed perioperatively in 4/5 cases. No recurrences after MMA embolization +/- surgery |
| 7.    | Kim                   | 2017 | Case series     | 20            | n.r.| n.r.| 6   | 0 0 20 0 Burr hole                                   | n.r n.r 6 0 0 0 | None            | MMA embolization alone at CSDH recurrence |
| 8.    | Matsumoto et al.      | 2017 | Case series     | 4             | n.r.| n.r.| n.r.| 0 0 4 Burr hole                                     | n.r n.r n.r 0 0 | None            | After second recurrence, MMA embolization +/- irrigation is not different to irrigation alone |
| 9.    | Link et al.           | 2017 | Case series     | 5             | 0  | 3  | 2   | 5 0 0 0 none                                         | 0 3 2 0 0 0 0   | None            | MMA embolization could present a primary treatment modality for symptomatic CDSH |

(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 |
|--------|--------------|------|-----------------|---------------|----|----|-----|--------------------------------------------------|----------------|-----------------|-------------|
|        |              |      |                 |               |    |    |      | Upright | Symptomatic CSDH (close to surgery to prevent recurrence) | Recurrent CSDH (after second surgery) |                  |             |
| 10.    | Sirh et al.  | 2018 | Case report     | 1             | 0  | 1  | 0   | 0      | 0 | 0 | 1 | 0 | Burr hole | 0 | 0 | 1 | 0 | 0 | None |
| 11.    | Ban et al.   | 2018 | Case series     | 72            | 25 | 28 | 19  | 27     | 45 | 0 | 0 | Burr Hole/ Craniotomy | 25 | 28 | 19 | 1 | 0 | None |
| 12.    | Link et al.  | 2018 | Case series     | 49            | 24 | 14 | 11  | 32     | 10 | 7 | 0 | Burr Hole/ Craniotomy | 24 | 14 | 11 | 4 | 0 | None |
| 13.    | Link et al.  | 2018 | Case series     | 6             | 1  | 4  | 1   | 0      | 0 | 6 | 0 | Craniotomy | 1 | 4 | 1 | 1 | 0 | None |
| 14.    | Okuma et al. | 2019 | Case series     | 17            | 5  | 8  | 4   | 0      | 17 | 0 | 0 | Burr hole | 5 | 8 | 4 | 0 | 0 | None |
| 15.    | Entezami et al. | 2019 | Case report     | 2             | 0  | 2  | 0   | 1      | 1 | 0 | 0 | Burr hole | 0 | 1 | 0 | 0 | 0 | None |
| 16.    | Entezami et al. | 2019 | Case report     | 1             | 1  | 0  | 0   | 1      | 0 | 0 | 0 | n.r. | 0 | 0 | 0 | 0 | 0 | None |

Case report. Prevention of recurrence in a patient with CSDH related leukemia. MMA embolization facilitates resolution and prevents reaccumulation of CDSH and is more effective than conventional treatment.

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. MMA embolization may represent an effective alternative to surgery. MMA embolization was not associated with recurrent CSDH or rehospitalization in our department in the current case series. Embolization was not associated with recurrent CSDH. MMA embolization feasible for CSDH treatment.
| S. No. | Author et al. | Year | Kind of article | Number of pts | Rt | Lf | Bil | Number of patients according indication for treatment | Kind of surgery | MMA embolization | Conclusions |
|-------|---------------|------|-----------------|---------------|----|----|-----|------------------------------------------------|----------------|----------------|-------------|
|       |               |      |                 |               |    |    |      | Upfront Symptomatic CSDH (close to surgery to prevent recurrence) |                  |                |             |
|       |               |      |                 |               |    |    |      | Recurrent CSDH | Recurrent CSDH (after second surgery) |                  |                |             |
|       |               |      |                 |               |    |    |      | Rt | Lf | Bil | Number of failures | Aborted procedures | Procedure related complications |             |
| 17.   | Nakagawa et al. | 2019 | Case series | 20 | n.r | 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 MMA can be useful for cases of recurrent CSDH in which anticoagulation or antiplatelet therapy is strongly indicated |
| 18.   | Waqas et al. | 2019 | Case series | 8 | 1 | 6 | 1 | 6 | 0 | 2 | 0 | n.r. | 1 | 6 | 1 | 0 | 0 | None | |
| 19.   | Wang et al. | 2019 | Case report | 2 | 0 | 0 | 2 | 1 | 1 | 0 | 0 | Burr hole | 1 | 1 | 0 | 1 | 0 | None | |
| 20.   | Piergallini et al. | 2019 | Case report | 2 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | n.r. | 0 | 1 | 1 | 0 | 0 | None | |
| 21.   | Kan et al. | 2020 | Case series | 138 | 54 | 70 | 15 | 93 | 0 | 45 | 0 | Burr hole/ Craniotomy | 69 | 85 | 15 | 9 | 0 | 2 | |
| 22.   | Eimad Sho tar et al. | 2020 | Case series | 89 | n.r | n.r | 15 | 0 | 89 | 0 | 0 | Burr hole | 15 | 4 | 8 | None | |
| 23.   | Rajah et al. | 2020 | Technical note | 1 | 0 | 1 | 0 | 1 | 0 | 0 | none | 0 | 1 | 0 | 0 | 0 | None | |
| 24.   | Mureb et al. | 2020 | Case series | 8 | 5 | 3 | 0 | n.r | n.r | n.r | 5 | 3 | 0 | 0 | 0 | None | |
| 25.   | Asham et al. | 2020 | Case report | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | Burr hole | 0 | 1 | 0 | 0 | 0 | None | |
| 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 |
|-------|------------------------|------|-----------------|---------------|----|----|-----|------------------------------------------------------|----------------|-----------------|-------------|
|       |                        |      |                 |               |    |    |      | Upright Symptomatic CSDH (close to surgery to prevent recurrence) |                | Rt   | Lf | Bil | Number of failures | Aborted procedures | Procedure related complications |             |
|       |                        |      |                 |               |    |    |      | Recurrent CSDH | Recurrent CSDH (after second surgery) |                |      |    |    | | | | |
| 26.   | Yokoya et al.          | 2020 | Case report     | 2             | 1  | 1  | 0   | 0          | 0          | 2          | 0             | Craniotomy       | 1   | 1  | 0   | 0   | 0   | None            | Benefit of MMA after recurrent CSDH treated with craniotomy |
| 27.   | Yajima et al.          | 2020 | Case series     | 18            | n.r| n.r| n.r | 3          | n.r        | n.r        | n.r        | Burr hole       | 0   | 0  | 0   | 0   | 0   | None            | Benefit of MMA embolization in preventing CSDH recurrence |
| 28.   | Shota et al.           | 2020 | Case report     | 1             | 0  | 0  | 1   | 0          | 1          | 0          | 0           | Burr hole       | 0   | 0  | 1   | 1   | 0   | None            | Development of AV fistula 3 months after MMA embolization |
| 29.   | Gomez-Paz et al.       | 2020 | Case series     | 23            | n.r| 18 | n.r | 23         | 0          | 0          | 0           | n.r           | 0   | 0  | 0   | 3   | 0   | None            | MMA alone in patients with or without midline shift but few symptoms can resolve CSDH |
| 30.   | Catapano et al.        | 2020 | Case series     | 35            | n.r| n.r| n.r | 20         | 8           | 9           | n.r         | Burr hole/craniotomy | 16  | 13 | 6   | 1   | 0   | 1           | MMA embolization of CSDH appears to be both safe and efficacious. |
| 31.   | Joyce et al.           | 2020 | Case series     | 121           | n.r| n.r| n.r | 51         | 17          | 53          | 0           | Burr hole/craniotomy | 69  | 52 | 30  | 9   | 3   | 3           | MMA embolization can be used safely and effectively as stand alone or as adjuvative treatment |
| 32.   | Ng et al.              | 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         | MMA embolization in addition with surgery reduces the time needed for resorption of the hematoma |
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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.[13] 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.[7,23] 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.[13,18,35,52] 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.[13] 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.[19,32]

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)?[9]

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.[7]
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.\(^1\)

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.\(^2\) 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.\(^3\) 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.\(^4\) 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.\(^5\) 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.\(^6\) 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.\(^7\)

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. 3 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

### 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                               |
| Hengli Wang | 2019  | Case report   | 1             | Prevention of enlargement                                                |
| Gary B. Rajah | 2020 | Technical note | 1             | Patient's preference                                                     |
| HirohsaYajima | 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
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.[31] 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;[24] 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.[7]

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,[7,9,13-15,19,20,24,35-37,48,50,51]
- As prophylaxis of a recurrence after a first surgery,[5,7,8,9,14,19,24,34-37,41,42,50]
- After a first recurrence to prevent further recurrence,[9,13,17,21,23,24,28,37,44,48,51,54]
- As an adjunctive treatment in case of a second surgery.[10,17,25,26,33,47]

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.[12,22,46]

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,[7] 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.[9]

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.[51]

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[17,25,26,33,47] then as a treatment aimed at preventing recurrence, mainly for patients under anticoagulant or antiplatelet medications.[19-21,52]
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 | Kind of surgery | Right | Left | Bilateral | Number of failures | Aborted embolizations | Procedure related complications |
|-----------------|------|------------------|---------------|-------|------|-----------|-------------------|-----------------------------------------------------------|---------------|----------------|-------|------|-----------|---------------------|--------------------------|-----------------------------|
| Kim et al.      | 2017 | Case series      | 20            | n.r.  | n.r. | 6         | 0                 | 0                                                           | 20            | Burr hole      | n.r.  | n.r. | 6         | 0                   | 0                        | None                        |
| Link et al.     | 2018 | Case series      | 49            | 24    | 14   | 11        | 32                | 10                                                         | 7             | Burr hole/ craniotomy | 24    | 14   | 11        | 4                   | 0                        | None                        |
| Ban et al.      | 2018 | Case series      | 72            | 25    | 28   | 19        | 27                | 45                                                         | 0             | Burr hole/ craniotomy | 25    | 28   | 19        | 1                   | 0                        | None                        |
| Nakagawa et al. | 2019 | Case series      | 20            | n.r.  | n.r. | 8         | 0                 | 0                                                          | 0             | Burr hole      | n.r.  | n.r. | 8         | 0                   | 0                        | None                        |
| Ng et al.       | 2020 | Clinical trial   | 21            | n.r.  | n.r. | 4         | 0                 | 21                                                         | 0             | Burr hole/ craniotomy | n.r.  | n.r. | n.r.      | 1                   | 1                        | None                        |
| Gomez-Paz et al.| 2020 | Case series      | 23            | n.r.  | 18   | n.r.      | 23                | 0                                                          | 0             | Burr hole      | n.r.  | 0    | 0         | 3                   | 0                        | None                        |
| Catapano et al. | 2020 | Case series      | 35            | n.r.  | n.r. | n.r.      | 20                | 8                                                          | 9             | n.r.           | 16    | 13   | 6         | 1                   | 0                        | 1                           |
| Rajah et al.    | 2020 | Case series      | 46            | 21    | 19   | 6         | 37                | 4                                                          | 5             | Burr hole      | 21    | 19   | 6         | 5                   | 2                        | None                        |
| Shotar et al.   | 2020 | Case series      | 89            | n.r.  | n.r. | 15        | 0                 | 89                                                         | 0             | Burr hole      | 15    | 4    | 8         | None                |                           |                             |
| Joyce et al.    | 2020 | Case series      | 121           | n.r.  | n.r. | n.r.      | 51                | 17                                                         | 53            | Burr hole/ craniotomy | 69    | 52   | 30        | 9                   | 3                        | 3                           |
| Kan et al.      | 2020 | Case series      | 138           | 54    | 70   | 15        | 93                | 0                                                          | 45            | 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. 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, or to patient’s preference as reported by Entezami et al. in 2021. 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., 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. 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.

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. 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.

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. and inclusion criteria by Catapano et al.

**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 antplatelet 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.

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.\textsuperscript{22,29,49}

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 \textit{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.\textsuperscript{34} 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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