Risk of recurrence of subdural hematoma after EMMA vs surgical drainage – Systematic review and meta-analysis

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Abstract

Objective: Chronic subdural hematoma (CSDH) is a common and debilitating neurological condition whose treatments, including burr hole drainage and craniotomy, suffer from high rates of recurrence and complication. Embolization of the middle meningeal artery (EMMA) is a promising minimally invasive approach to manage CSDH in a broad set of patients.

Methods: To evaluate the efficacy and safety of EMMA, a database search was conducted including the terms “subdural hematoma; embolization; embolized; middle meningeal” was performed and yielded a total of 260 results. Following exclusion based on predefined criteria, a total of four studies were identified and outcomes including recurrence rates and complication rates were extracted for analysis.

Results: Four studies including intervention and control groups were included with a total of \( n = 888 \) patients. The relative risk of CSDH recurrence in the EMMA (3.5%) compared to control group (23.5%) was significantly reduced when EMMA was performed (risk ratio = 0.17; 95% confidence interval (CI) 0.05–0.67). In addition, rates of complication were not significantly different between patients with conventional therapy and those who received EMMA (OR = 0.77; 95 confidence interval (CI) 0.3–1.99).

Conclusion: Based on limited data, EMMA reduces the risk of recurrence by 20% compared to surgical treatment for CSDH.

Keywords
Embolization, chronic subdural hematoma, surgical drainage, craniotomy

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Introduction

Chronic subdural hematoma (CSDH) is a common neurologic condition with an incidence reported between 1.72 and 20.6 per 1,00,000 per person per year.\(^1\) The incidence increases progressively with age and is increased by a factor of 3.5 over the age of 70 and 6.5 over the age of 80.\(^1\)

CSDHs are commonly treated with burr hole craniotomies for evacuation of the hematoma and closed system drainage. Despite aggressive treatment, the clinical course is frequently complicated by recurrence with rates reported from 7.5 to 29%.\(^2,3\) Recurrence is more likely in patients with bilateral hematomas, significant atrophy or use of anticoagulation. The need for reoperation complicates recovery and rehabilitation in a frequently elderly and frail population. The relatively high rate of recurrence is believed to arise from the pathophysiology of CSDH. In particular, angiogenesis within the membranes of the CSDH forms friable blood vessels liable to rupture.\(^4\) Further, activation of fibrinolytic pathways may further increase the risk of bleeding from these highly susceptible vessels. While surgical therapy remains the mainstay of treatment for symptomatic CSDH several medical therapies have been investigated without the emergence of a clear or effective alternative. Therapies that have been investigated include the use of corticosteroids, statins, anti-fibrinolytic medications and ACE-inhibitors.\(^5\)–\(^8\)

Embolization of the middle meningeal artery (EMMA) provides an alternative treatment methodology that more directly address the likely underlying pathophysiology of CSDH.\(^9\) Early reports of EMMA focused on cases without alternative treatment

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options; however, more recently there has been significant interest in broadening the use of EMMA due to its minimally invasive nature and apparent effectiveness.\(^\text{10}\)

It is still unclear the risk of recurrence in the patients undergoing EMMA compared to those undergoing surgical drainage. The difference in the recurrence risks is the key parameter for planning of any future studies. We perform a systematic review to evaluate the rates of recurrence of CSDH when treatment with EMMA compared with conventional burr holes craniotomy.

**Methods**

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines in order to guide the literature search, inclusion and exclusion of articles, and final statistical analysis of included studies.

**Inclusion criteria**

*Study type:* Any prospective or retrospective case series or clinical trials with at least five patients with CSDH, where outcome was compared between those treated with EMMA vs those treated with surgical drainage.

*Patient type:* Patients of all ages with the diagnosis of chronic subdural hematoma.

*Intervention:* EMMA using any embolic material.

*Comparator:* CSDH patients undergoing surgical drainage.

*Outcome measures:* recurrence of CSDH and safety of EMMA or surgical drainage.

*Follow up period:* At least three months from the last treatment

**Exclusion criteria**

Studies researching acute SDH; studies with no comparator group of patients undergoing surgical drainage; case reports and case series with total number of patients less than five, review articles and conference abstracts were excluded.

**Search strategy**

PubMed (MEDLINE) \((n = 85)\), Embase \((n = 101)\) and Scopus \((n = 74)\) databases were searched for studies reporting the outcome of EMMA for treatment of CSDH, with the restriction of English language. The search strategy included a combination of Medical Subject Headings terms such as subdural hematoma; embolization; embolization; embolized; middle meningeal; meningeal and was performed by a librarian at the University of Manitoba medical library. In addition to online database searching, reference lists of all included studies and previous reviews were also screened.

**Data collection and analysis**

Two researchers (JD and JS) independently used Covidence for the primary and secondary screening (title/abstract and full text, respectively) and data extraction to streamline the production of standard intervention reviews. The titles and abstracts were screened and were categorized as ‘Yes’, ‘No’ and ‘Maybe’. For those categorized as ‘Yes’ and ‘Maybe’, a full text review was done to assess the inclusion of the studies. If eligibility was doubtful, articles were discussed with the investigators and were included or excluded based on consensus. The studies comparing the recurrence rate and complications associated with EMMA as compared to surgical intervention were included in the meta-analysis. Studies with less than five patients in a group were excluded from the meta-analysis. Single arm assessing results from EMMA only were not included in the meta-analysis. Data were then extracted from the included studies using a standard extraction form with characteristics of the trials, participants, interventions and outcomes. Data on all relevant variables were collected.

**Quality assessment**

The quality of included articles was assessed independently by two blinded authors using Cochrane risk of bias criteria. Cochrane risk of bias criteria included assessment of sequence generation; allocation concealment; blinding of participants and study personnel; blinding of outcome assessors; incomplete outcome data, selective outcome reporting and other sources of bias.

**Meta-analysis**

A quantitative synthesis, supplemented by a qualitative discussion was used, for a thorough and accessible amount of the available data. For the quantitative synthesis, meta-analysis was conducted synthesizing risk ratio of recurrence and safety in patients undergoing EMMA vs those who did not. The efficacy of EMMA was calculated using a random effects generic inverse variance meta-analysis. The Cochrane Collaboration statistical software, Review manager (Revman 5.4) was used to conduct the meta-analysis and forest plots were generated. Pooled estimates and 95\% confidence interval (CI) were calculated.

**Ethical approval**

“All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964
Helsinki declaration and its later amendments or comparable ethical standards”.

Results
The search and selection strategy is illustrated in Figure 1. Only four studies were included for the final meta-analysis. These were the only studies that reported a control group where patients underwent surgical drainage for their CSDH. The details of these studies are given in Table 1. The studies were conducted in Korea and France.

Quality of evidence
Quality of evidence was generally low. All the studies included had a mixed prospective intervention group and retrospective historical control group with one randomized control trial. The randomized control trial was a pilot study and was underpowered for any conclusion. Most studies did not have the blinded participants and outcome assessors.

Patient characteristics
A total of 888 patients were included in the analysis of which the majority were male (n = 639/888; 72%) (Table 2). The mean age was 72 years (age range: 60–84 years). Within the population, 45% were on antiplatelet agents or anticoagulation. Significantly higher proportion (p < 0.001) of patients in the EMMA group (n = 116/200, 58%) were on antiplatelet agents or anticoagulation as compared to (n = 280/688, 41%) in the control group.

Treatment characteristics
Conscious sedation was used in the vast majority of cases with general anesthesia in only three cases. Five or six french guide catheters were used in all cases. A variety of different microcatheters were used including Prowler 10, SL10 and Headway 21. Embolization was performed with PVA 150–250 μm (n = 39/200; 20%), Contour 150–250 μm (n = 72/200; 36%), triacyl gelatin microspheres 300–500 μm (n = 81/200; 42%) with associated coiling in (n = 27/200; 14%). EMMA was the sole treatment in 14% (27/200) of the EMMA group, while all other had associated surgical drainage.

Follow-up
The duration of follow up varied but all studies reported the follow up at 90 days. CT scan of head was done to diagnose and assess recurrence.

Outcomes and complications
In the four included studies the rates of recurrence were compared across the population undergoing EMMA with or without surgical drainage vs those treated only with surgical drainage. There was 3.5% (n = 7/200) recurrence of SDH in the EMMA group as compared to 23.5% (n = 162/688) in those treated with surgical drainage alone. Meta-analysis demonstrated that the recurrence risk was significantly lower in the EMMA group as compared to the surgical drainage alone group (risk ratio = 0.17; 95% confidence interval (CI) 0.05–0.67; p = 0.01; I² = 50%) (Figure 2). The absolute risk reduction for recurrence was 20% with a NNT of five patients.

Figure 1. Flow diagram using PRISMA methodology showing stages of article selection and final studies included for meta-analysis.
Rates of complication associated in EMMA group was 5% (n = 10/200) vs 5.5% (n = 38/688) in the surgical drainage only group. Meta-analysis demonstrates the complication between groups was not significantly different (OR = 0.77; 95% CI 0.3–1.99; p = 0.59). Complications reported were seizures (n = 13), wound infections (n = 11), periprocedural subdural/epidural hematomas (n = 8), cerebral infarcts (n = 8), unrelated infection (n = 3), ICH (n = 4), angina (n = 1), and delirium (n = 1).

Table 1. Characteristics of studies involved and the patient populations in each study.

| Study design | Embolization | Inclusion criteria | Primary outcome | N   | Female | Age | Trauma | Bilateral | Thickness |
|--------------|--------------|--------------------|-----------------|-----|--------|-----|--------|-----------|-----------|
| Kim¹¹        | Prospective and retrospective groups, non randomized | Adjunctive treatment | Recurrence after surgery | 20 6 72 9 | 8 6 18 |
| Ban et al.¹² | Prospective and retrospective, non randomized | Primary treatment | All new CSDH | 72 24 69 29 | 45 19 20 |
| Shotar et al.¹³ | Prospective and retrospective, non randomized | Adjunctive treatment | High risk for recurrence | 89 21 74 71 | NR 15 NR |
| Ng et al.¹⁴ | Prospective and randomized | Adjunctive treatment | Symptomatic CSDH | 19 9 77 7 | 12 3 NR |

Discussion

Level of evidence was generally low; mainly because all the included studies had a retrospective control arm except for only one underpowered randomized control trial. Patients’ randomization was not clear. Most studies did not have the blinded participants and outcome assessors.

Major findings

Efficacy

Four studies with a total of 888 patients undergoing treatment for CSDH were included in the review. Only 200 of these patients underwent EMMA. The recurrence was reported on a CT head at three months after treatment. Recurrence of CSDH was objectively reported in 23.5% of patients who underwent surgical drainage only. This was reduced to 3.5% in those who underwent EMMA with or without surgical drainage. Those who underwent EMMA had a significantly (p = 0.01) lower risk of recurrence (0.17) at three months from the time of treatment.
Complications \( (p = 0.59) \) and mortality \( (p = 0.86) \) between the two comparison groups were not significantly different. Perioperative complications unrelated to recurrence have been reported to occur with rates of 2.5–9.3\% depending on the choice of surgical technique.\(^\text{15}\) In some series non recurrence complication rates up to 30\% have been reported.\(^\text{16}\) The lower complication rate in the surgical group could be due to the historical nature of the controls in most of our studies.

In addition, high rates of recurrence from 7.5 to 9\% frequently necessitate repeat surgery for satisfactory resolution of the hematoma. The CSDH patient population is an elderly, with multiple comorbidities and frequent use of antiplatelet agents/anticoagulation and as such minimally invasive options for management of the CSDH are desirable. In the context of patients on antiplatelet agents and anticoagulants EMMA was also superior.

The use of antiplatelet and/or anticoagulant medications is increasingly common for neurologic, cardiac and vascular indications. In this study, overall 46\% of patients were using antiplatelet agents/anticoagulation. The rates were significantly higher \( (p < 0.001) \) in the EMMA group at 58\% as compared to 41\% in the control group. In many cases, the risks of withdrawal of anticoagulation to facilitate CSDH treatment must be weighed against the risk of thrombotic events associated with cessation of anticoagulation. EMMA can be safely performed without withdrawal of anticoagulation and therefore is an ideal method to manage SDH in high risk groups.

One study included, Ban et al.\(^\text{12}\) demonstrated that in 27 patients, EMMA alone may be satisfactory treatment for asymptomatic CSDH. In our study only one study reported EMMA as the primary treatment for CSDH. In the other three studies, EMMA was an adjunctive treatment. Until high level evidence is seen favoring EMMA for treatment of CSDH, the primary treatment of CSDH with EMMA alone will remain controversial. A well powered randomized control trial is needed to answer this question. Two randomized control trials are being planned (EMBOLISE – ClinicalTrials.gov Identifier:...
More studies are required on the comparison of embolic agents.

Limitations
The limitation of our systematic review is mainly due to low quality of the included literature. The majority of the studies suffered from high risk of bias especially for sequence generation, allocation concealment and blinding of participants and other personnel for all outcomes.

How is this different from other reviews. To the best of our knowledge this is the first systematic review to report the recurrence risk of CSDH treated with EMMA vs surgical drainage alone. A well-planned randomized control trial is needed to assess the efficacy of EMMA in preventing recurrence of CSDH. To plan such a randomized control trial and for sample size calculation of such a trial, the absolute difference in the recurrence risk between the two treatment arms is needed. Our study is the first study which reports this absolute recurrence risk difference.

Conclusions
Within the limitation of low-quality studies included in the systematic review and meta-analysis, our study showed 20% reduction in the recurrence risk in patients of CSDH treated with EMMA compared to those treated with surgical drainage alone.

Authors’ contribution
JD – Data collection, analysis and manuscript preparation and review; JL – Search and manuscript review; JJS – Conceptualization, data collection, analysis and manuscript preparation and review.

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Ethical approval
“All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

Informed consent
Not applicable.

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