How to remove those bloody collections: Nonsurgical treatment options for chronic subdural hematoma

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Abstract:

Chronic subdural hematoma (CSDH) is one of the most prevalent neurosurgical disorders. Patients with CSDH commonly present with altered mental status, focal neurological deficit, and/or headache. The first-line treatment for CSDH is surgical evacuation. Although the surgical procedures for CSDH have been considered relatively "straightforward," they are not without any risk. The elderly are especially prone to show poor surgical outcomes. To make matters worse, many elderly patients are on anticoagulants and antiplatelet agents, increasing the risk of re-bleeding before and after surgery. These complications have led clinicians to search for nonsurgical alternatives. Dexamethasone should be used with caution for selected patients given its side effects. Tranexamic acid may be utilized as an adjunct therapy to surgery, but more randomized clinical trials are needed to evaluate its definitive efficacy. Interesting results of middle meningeal artery embolization (MMAE) have been reported from case studies. However, the risks associated with MMAE, including intracerebral hemorrhage, stroke, and vasospasm, have not been properly studied yet. The clinical benefits of atorvastatin and angiotensin-converting enzyme inhibitors are uncertain for CSDH. In conclusion, surgical intervention continues to be the first-line treatment while nonsurgical treatment options may be considered an adjunct therapy especially for recurrent hematoma or to reduce the volume of a hematoma.

Keywords:

Angiotensin-converting enzyme inhibitors, atorvastatin, chronic subdural hematoma, dexamethasone, middle meningeal artery embolization, nonsurgical therapies, tranexamic acid

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Introduction

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical diseases. Its annual incidence is 20.6/100,000.[1] CSDH typically occurs after trauma. Patients with CSDH may present with altered mental status, focal neurological deficit, and/or headache. The first-line treatment for CSDH is surgical evacuation. Different surgical procedures are available, such as percutaneous bedside twist-drill drainage and burr-hole procedure. There is no significant difference in outcome between these procedures though irrigation and postoperative drainage are known to have clear clinical benefit for CSDH.[2]

Although the surgical interventions for CSDH have been considered relatively "straightforward" and effective, they are not without any risk. Elderly patients are especially vulnerable to poor surgical outcomes. Functional outcome, assessed by the modified Rankin Score, notes only 71.6% good but 28.4% poor outcomes for elderly patients after surgery and about 30% of them require some help at discharge.[3] Moreover, this poor outcome rate increases to 37.4% and 56.8% for patients in their 80s and 90s, respectively. The recurrence rate of CSDH ranges from 0.36% to 33.3%.[1] Those who are in the age group of 75–80 years show the highest recurrence rate.[4]

To make matters worse, many elderly patients are on anticoagulants and antiplatelet agents. More than 30 million prescriptions for warfarin are written every year and use of new oral anticoagulants, such as rivaroxaban and dabigatran, is increasing.[5,6] Both anticoagulant and antiplatelet drugs are strongly associated with increasing incidence of CSDH.[7] Rust *et al*.[8] note that the risk of developing CSDH is 42.5 times higher in patients treated with warfarin. Vitamin K and fresh frozen plasma are available to normalize the international normalized ratio in the preparation of surgery for those being treated with anticoagulants. However, elderly patients may not favorably tolerate the hemodynamic changes, such as fluid overload, with these antidotes. Although prothrombin complex concentrate and recombinant factor VIIa are other options, there are no evidence-based guidelines for patients with CSDH who are on antithrombotic agents at this point. The increased postoperative risks and recurrence of CSDH associated with antithrombotic therapy have encouraged clinicians to search nonsurgical alternatives for CSDH.

Pathophysiology of Chronic Subdural Hematoma

CSDH was initially thought to be formed by tearing the bridging veins from the brain parenchyma to the draining dural–venous sinuses. The injured bridging veins would accumulate venous blood in the subdural space. However, this theory was questioned with inconsistencies of how patients with CSDH presented clinically. For instance, numerous patients with head injury initially showed normal head imaging studies but developed CSDH weeks and months later. A slow venous hemorrhage would accumulate enough volume to cause the symptoms in matters of days. This suggested acute hemorrhage was not the only source of CSDH. In addition, blood collections consisting of old blood products in the subdural space were observed to grow larger slowly over time.

Inflammation was later believed to play critical roles in the development of CSDH. Virchow[9] coined the term "pachymeningitis haemorrhagica interna" to note chronic inflammation in the dura from fibrin exudation and development of new capillaries in response to bacterial infection. This inflammatory response was, however, not limited to infection but any cellular injury. In 1946, Inglis[10] found a layer of connective tissue cells on the dura, later named "dural border cells." Injury to the dural border cells initiated recruiting inflammatory cells and formed membranes in the subdural space [Figure 1]. The inflammatory cells were pro-angiogenic, developing immature blood vessels in the blood collection cavity. The newly formed blood vessels were highly permeable, allowing intravascular
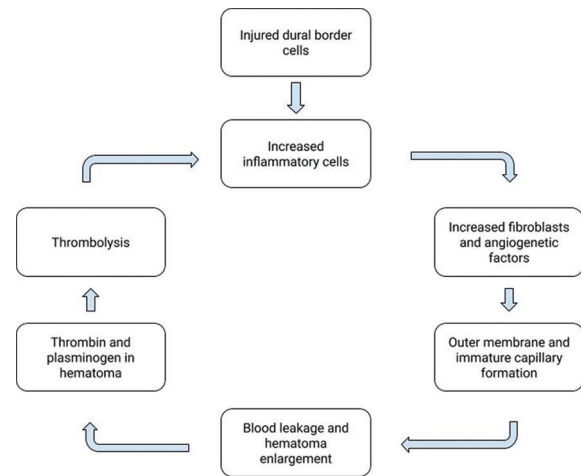

Figure 1: Development of chronic subdural hematoma

fluid to exudate. Micro-hemorrhage occurred from the immature vessels, forming blood clots. Thrombolysis subsequently dissolved the newly formed clots, enlarging the blood collection and rendering the inflammatory response persistent. This understanding of recursive inflammatory response in the development of CSDH provided targets of nonsurgical therapies [Figure 2].

Corticosteroids

Corticosteroid produces well-known anti-inflammatory effects by affecting the differentiation and function of immune cells, such as macrophages and B- and T-cells, and mediating transcription of inflammatory proteins, such as chemokines and cytokines. Steroids modify capillary endothelial cells and the tight junctions by regulating expression of the occludin gene.[11] This promotes impermeability of the blood–brain barrier, decreasing the permeability of the vessels in CSDH.[12] In addition, the level of matrix metalloproteinases, a critical enzyme responsible for modulating inflammation, angiogenesis, and vascular permeability, has been found to decrease with usage of steroids.[13] Nonetheless, corticosteroids are not without risk. The commonly known side effects include worsening open-angle glaucoma, ocular hypertension, and hyperglycemia.

In 1976, Glover and Labadie reported histological evidence of smaller blood clots and the absence of neomembrane formation of CSDH when dexamethasone was injected to rats.[14] Sun *et al*.[15] collected 112 patients with CSDH and treated 26 patients only with dexamethasone. Only one patient from the dexamethasone treatment group required a surgical drainage. However, the study noted no significant difference in the rate of re-drainage between the groups treated with dexamethasone versus surgery. Another retrospective study reviewed 122 patients with CSDH, in which 101 patients were treated with dexamethasone alone.[16] The outcome of
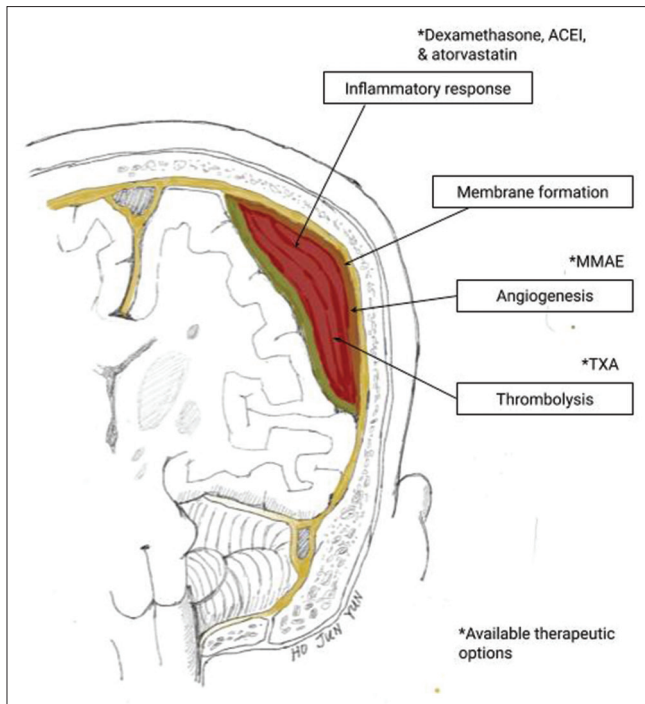
Figure 2: Targets of nonsurgical therapies

the dexamethasone group was comparable to that of the surgery group (favorable outcome of 96% vs. 93.9%, respectively). Berghauser Pont et al.[17] retrospectively analyzed 496 patients with CSDH and found that extended preoperative steroid use was associated with lower recurrence rates. Unfortunately, these studies were either Level 2 or 3 evidence to support the clinical use of dexamethasone. A pilot, placebo-controlled, randomized trial was attempted. The trial involved twenty patients with CSDH but was prematurely terminated due to significant complications from dexamethasone.[18] The authors of the trial indicated no clear beneficial effect of dexamethasone against placebo.

Several Level 1 evidence studies have shown mixed findings about dexamethasone. A prospective randomized clinical trial including 47 patients concluded that dexamethasone therapy with surgical drainage was safe and could significantly decrease recurrence rate.[19] On the other hand, Almenawer et al.[20] published a meta-analysis of 34,829 patients with CSDH. The study noted higher morbidity associated with the adjuvant use of steroid, and there was no significant improvement in the recurrence rate of CSDH. Finally, Holl et al.[21] reviewed 796 studies to specifically compare the efficacy of corticosteroid alone, corticosteroid as an adjunct to surgery, and surgery alone. This meta-analysis concluded that corticosteroids may be effective as an adjunct therapy to surgery. More importantly, the authors noted that the risk of bias of the studies was high and warned the results to be interpreted with caution.

Tranexamic Acid

As previously mentioned, one component of developing CSDH is small hemorrhages associated with the newly formed immature vessels. The micro-hemorrhages activate the coagulation cascade, converting prothrombin to thrombin. Thrombin subsequently cleaves fibrinogen to fibrin that forms clots. The clots are then broken down to fibrin/fibrinogen degradation products via fibrinolysis. Plasmin plays the primary role in fibrinolysis, and it is formed from plasminogen by tissue plasminogen activator. Fibrinolysis occurs actively in CSDH fluid, and this has been thought to contribute to continued hemorrhage and CSDH expansion.[22]

Tranexamic acid (TXA) is a synthetic form of lysine. TXA inhibits the conversion of plasminogen to plasmin by binding to the lysine receptor sites of plasminogen. Kageyama et al.[23] first published a retrospective study of 18 patients with CSDH who were treated with 750-mg TXA daily instead of surgery. The study radiographically demonstrated significant reductions of the median hematoma volume (55.6 ml to 3.7 ml). There was no reported recurrence. This study was later criticized due to its retrospective design; the study excluded patients on anticoagulant or antiplatelet therapy. Nevertheless, two other studies later demonstrated promising results of TXA. A retrospective analysis of 14 patients who were treated with TXA after surgery showed additional 91.31% reduction of the residual hematoma volume, whereas the surgical intervention initially reduced the volume by 40.74%.[24] Stary et al.[25] described three patients who developed recurrent subdural hematomas after they had surgery. The authors found complete resolution on imaging studies and clinical improvement after the recurrent subdural hematomas were treated with TXA.

Yamada and Natori[26] performed the first prospective randomized clinical trial. They included 193 patients who underwent burr-hole surgery. These patients were then divided into three groups treated with TXA, goreisan, and observation. The study found no difference in the recurrence rate, but the residual hematoma volume was significantly smaller in the TXA group. TXA in Chronic Subdural Hematomas is a double-blinded randomized study currently ongoing. The study consists of 130 patients treated either with TXA or placebo.

Middle Meningeal Artery Embolization

Middle meningeal artery embolization (MMAE) is a relatively new technique for treating CSDH. MMAE is believed to reduce immature capillary development and membrane formation in CSDH and subsequently decreases the repeated cycles of subdural re-bleeding. This hypothesis is based on the presence of irregular

branches of MMA radiographically demonstrated in CSDH.[27]

In 2000, Mandai et al.[28] first published a case report of a 59-year-old male who had CSDH complicated by coagulopathy from liver cirrhosis. The patient underwent several surgical drainages and failed to show a successful outcome. Eventually, MMAE was performed which resolved the patient's recurrent CSDH. Several case reports and series were subsequently published, advocating the benefit of MMAE especially for recurrent CSDH.[29-31] Hirai et al.[32] presented two patients under anticoagulation therapy whose recurrent CSDHs were completely resolved after MMAE. One patient had a computed tomography study immediately after MMAE which showed increased density of the subdural hematoma, indicating the extravasation of contrast media from the MMA. Link et al.[33] included sixty CSDH cases where fifty were treated primarily by MMAE. Of these 50 cases, the study reported 4 cases (8.9%) with recurrent subdural hematoma which required surgery, 31 (68.9%) with resolution or reduction in size of hematoma >50%, and 41 (91.1%) with long-term success rate.

Ban et al.[27] published the only available prospective study including 72 patients with CSDH. Twenty-seven patients were treated only with MMAE and 45 were treated traditionally with surgery followed by MMAE. The trial reported complete resolution of hematomas in all patients treated only with MMAE. Only one patient of the group treated by surgery and MMAE developed recurrent subdural hematoma. Although the results were promising, the trial was later criticized due to its study design, which eventually nullified the level of evidence. The first randomized clinical trial is currently recruiting patients in the USA.[34]

Atorvastatin

Atorvastatin has been proposed as a nonsurgical therapy for CSDH due to its anti-angiogenic effects (i.e., inhibition of vascular endothelial growth factor [VEGF] and interleukin-8), anti-inflammatory effects (i.e., reducing tumor necrosis factor-α and monocyte chemoattractant protein 1), and fibrinolytic effect by reducing collagen deposition.[35] Additionally, atorvastatin is relatively safe and cost-effective, compared to surgery.

Chan et al.[36] note that atorvastatin showed a lower rate of deterioration with CSDH and the need for burr-hole drainage. However, this was a retrospective cohort comparison study and the conclusion was based only on 12 patients. Liu et al.[37] performed a placebo-controlled observation study on eighty patients that showed atorvastatin promoting the resolution of CSDH and reducing the need of surgery. Unfortunately, this study

was retracted due to serious errors in data analysis and exaggerated results. The same group later conducted a prospective randomized trial on 168 patients with CSDH and concluded that atorvastatin may decrease the risk of recurrence.[38] However, this paper was retracted as well, ultimately clouding the efficacy of atorvastatin for CSDH.

Angiotensin-Converting Enzyme Inhibitors

One of the side effects of angiotensin-converting enzyme inhibitors (ACEIs) includes anti-angiogenesis. This feature of ACEIs has triggered clinicians to postulate potential roles in lowering recurrence rate and even development of CSDH. Weigel et al.[39] reviewed 310 patients who had undergone surgical procedures for their CSDH. The patients were divided into two groups, based on whether they were being treated with an ACEI, and measured VEGF. The study found a lower recurrence rate associated with ACEI (5% vs. 18%) and significantly lower VEGF content in the group treated with ACEIs (mean, 8,891 pg/ml vs. 22,565 pg/ml; $P = 0.0116$). Poulsen et al.[40] performed a randomized trial including 47 patients who had undergone burr-hole procedures. The patients were given either perindopril or placebo postoperatively. When the sizes of the CSDH were measured before and 6 weeks after surgery, there was no difference between the perindopril-treated and placebo groups. The trial concluded that ACEIs do not decrease the risk of CSDH recurrence either.

Conclusions

Our better understanding of CSDH has led to exploring numerous nonsurgical treatment options. Dexamethasone may be effective as an adjunct to surgery. Its clinical benefits are comparable to surgery alone. However, more Level 1 evidence studies are needed to support the clinical use of dexamethasone. Given the known side effects, dexamethasone should be used with caution for selected patients. Further randomized clinical trials are needed to evaluate the definitive efficacy of TXA. Nonetheless, available evidence indicates reduction of hematoma volume and minimal complications associated with TXA. TXA may be considered an adjunct therapy to surgery for now. Numerous cases have reported the benefit of MMAE, especially for recurrent CSDHs. Further studies are needed to properly assess the risks associated with MMAE, such as intracerebral hemorrhage, stroke, and vasospasm. Clinical benefits from atorvastatin and ACEIs are unclear to warrant its usage for CSDH at this point.

Surgical intervention remains to be the first-line treatment for CSDH. While more research is being

conducted, nonsurgical therapies may be considered an adjunct to surgery; these adjunct therapies may be valuable especially for recurrent hematoma or to reduce the volume of hematomas. Developing new guidelines, including these nonsurgical therapies, is desirable. Meanwhile, surgeons continue to play key roles in making individualized treatment decisions for each patient.

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Conflicts of interest
There are no conflicts of interest.

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