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Review Article

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Medical Management of Chronic Subdural Hematoma

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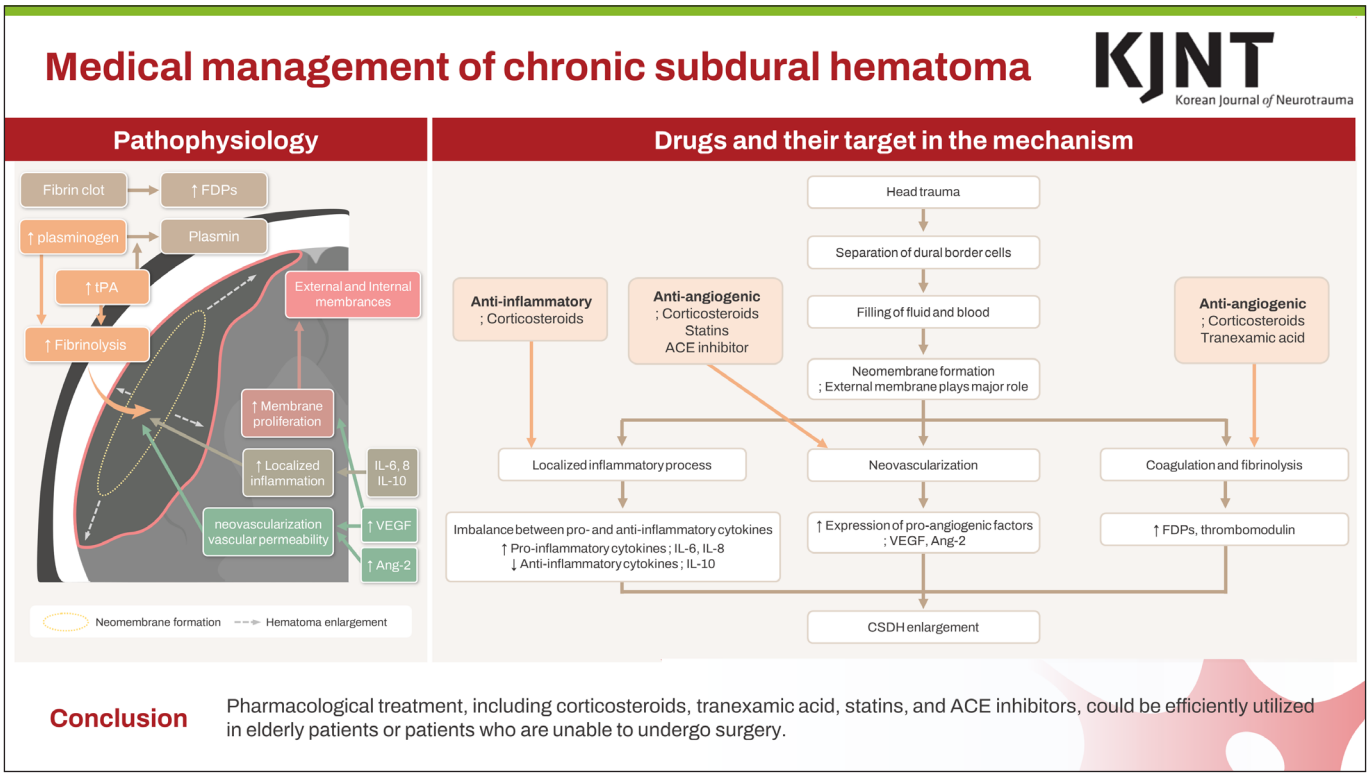
ABSTRACT

Chronic subdural hematoma (CSDH) is a commonly encountered disease in the field of neurosurgery, typically resulting from head trauma. Several medical treatments have been introduced to manage patients with CSDH though surgical drainage is the main strategy to manage symptomatic patients. This review is aimed to meticulously examine contemporary pharmacological approaches, based on a thorough understanding of CSDH pathophysiology. Finally, the review offers a glance into future perspectives to enhance the management of CSDH.

Keywords: Chronic subdural hematoma; Corticosteroid; Tranexamic acid; Statin; ACE inhibitor

GRAPHICAL ABSTRACT



INTRODUCTION

Chronic subdural hematoma (CSDH), frequently observed in elderly patients, is a prevalent condition in the field of neurosurgery, typically resulting from head trauma. There are approximately 1.7 to 58 cases of CSDH per 100,000 people per year.[28]

Due to the aging population, the incidence of CSDH has been on the rise. In elderly individuals, progressive cerebral atrophy contributes to the gradual development of hematomas as a result of head trauma. Additionally, elderly patients often have comorbidities and are prescribed antiplatelet and anticoagulant medications, further contributing to the increased occurrence of CSDH.[1,11,28,29]

Symptomatic CSDH is typically managed with surgical intervention, however, performing surgery can pose challenges in cases involving elderly patients who are advanced in age and undergoing anticoagulant therapy. And approximately 27% to 33% of patients experience recurring hematoma, and the mortality rate among surgically treated patients can reach as high as 24% to 32%. The presence of these surgical limitations makes the pursuit of a safe and effective non-surgical treatment for CSDH.[7,11,13]

In this article, we explore the pathogenesis of CSDH and examine medical managements that have been developed and clinically evaluated based on the established pathways associated with CSDH.

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PATHOGENESIS

The development of CSDH involves a complex and multifactorial pathogenesis. Although a definitive mechanism for CSDH has yet to be established, several potential pathways have been explored (**FIGURE 1**).[27]

Between the dura mater and the arachnoid mater, there exists a layer of dural border cells with expanded extracellular space that contains bridging veins. The bridging veins in individuals with brain atrophy, such as the elderly or alcoholics, occur stretching as a result of the separation between the arachnoid and the dura mater.[17,18,29] After the pathological separation of the dural border cells, two membranes develop, creating a new subdural cavity that gradually fills with fluid and blood.[11,29] Typically, the internal membranes are described as primarily consisting of collagen and fibroblasts, lacking significant functionality in promoting the growth of CSDH. On the other hand, the external membrane plays a more critical role in stimulating the growth of CSDH. It consists of layers of fibroblasts and collagen fibers, along with the presence of inflammatory cells like neutrophils, lymphocytes, macrophages, and eosinophils.[4]

CSDH is also characterized as a localized chronic inflammatory disorder that sustains itself over time. There is a noticeable difference between the pro-inflammatory cytokines in the CSDH fluid and those in the circulating blood, such as interleukin (IL)-6 and IL-8.[6] Meanwhile, CSDH contains anti-inflammatory cytokine, IL-10, which inhibits the pro-inflammatory cytokines. CSDH formation and enlargement are influenced by the disparity between those cytokines.[4]

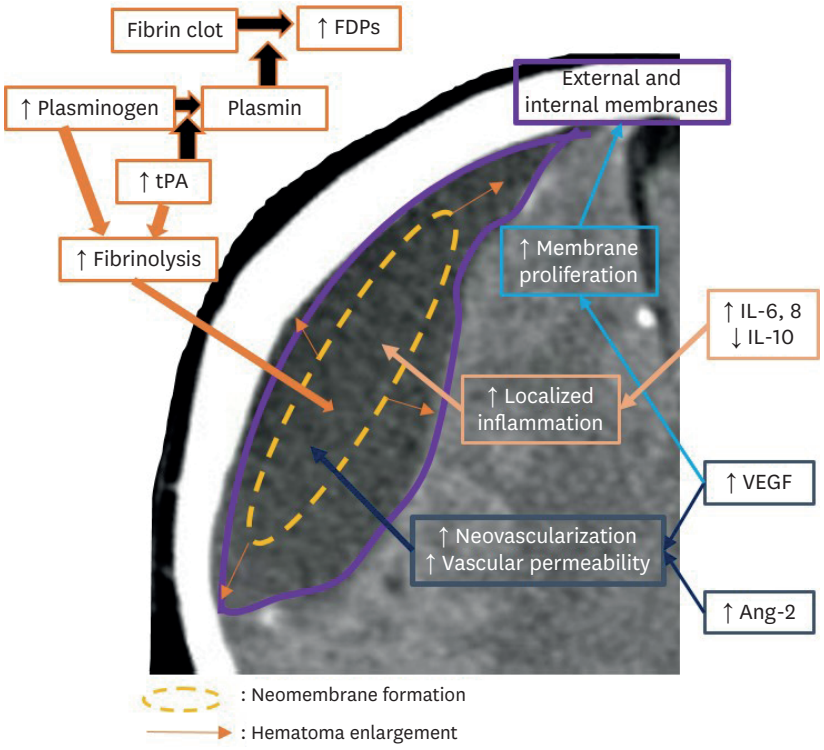

FIGURE 1. Pathogenesis of chronic subdural hematoma.
FDP: fibrinogen degradation product, tPA: tissue plasminogen activator, IL: interleukin, VEGF: vascular endothelial growth factor, Ang-2: angiopoietin-2.

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Several mediators involved in the formation of CSDH primarily contribute to the development of new blood vessels, thus serving as a source of bleeding from the CSDH membranes.[5] Vascular endothelial growth factor (VEGF), a crucial pro-angiogenic factor, is responsible for increasing microvascular permeability through the increase in microvascular endothelial growth factor. The presence of a substantial amount of VEGF has indeed been observed in CSDH.[7,16] The expression of VEGF is notably increased in the outer membrane and is closely associated with the recurrence of CSDH. The proangiogenic factor angiopoietin-2 (Ang-2) is also found to be highly expressed in CSDH. Elevated levels of Ang-2 expression can lead to the formation of inadequately developed vessels that exhibit increased permeability.[4,7]

In the formation of CSDH, bleeding plays a crucial role involving coagulation and fibrinolysis process. The process of the coagulation cascade entails the conversion of prothrombin into thrombin. Thrombin, in turn, has the ability to break down fibrinogen into fibrin, facilitating the formation of blood clots. Fibrinolysis is the opposite process, involving the breakdown of fibrin into fibrin/fibrinogen degradation products (FDPs), thereby promoting the breakdown of blood clots. The elevated levels of FDPs detected in CSDH fluid are believed to indicate excessive fibrinolysis, leading to ongoing hemorrhage. Thrombomodulin is an additional substance that can promote fibrinolysis and has been identified in significant concentrations within CSDH fluid. There is a suggestion that thrombomodulin is consistently released during the formation of CSDH as a result of repeated vessel injury.[4]

MEDICAL MANAGEMENT

Based on pathophysiologic mechanisms, medical treatment has a crucial role in CSDH management (**FIGURE 2**). Drugs, including corticosteroids, tranexamic acid (TXA), statins,

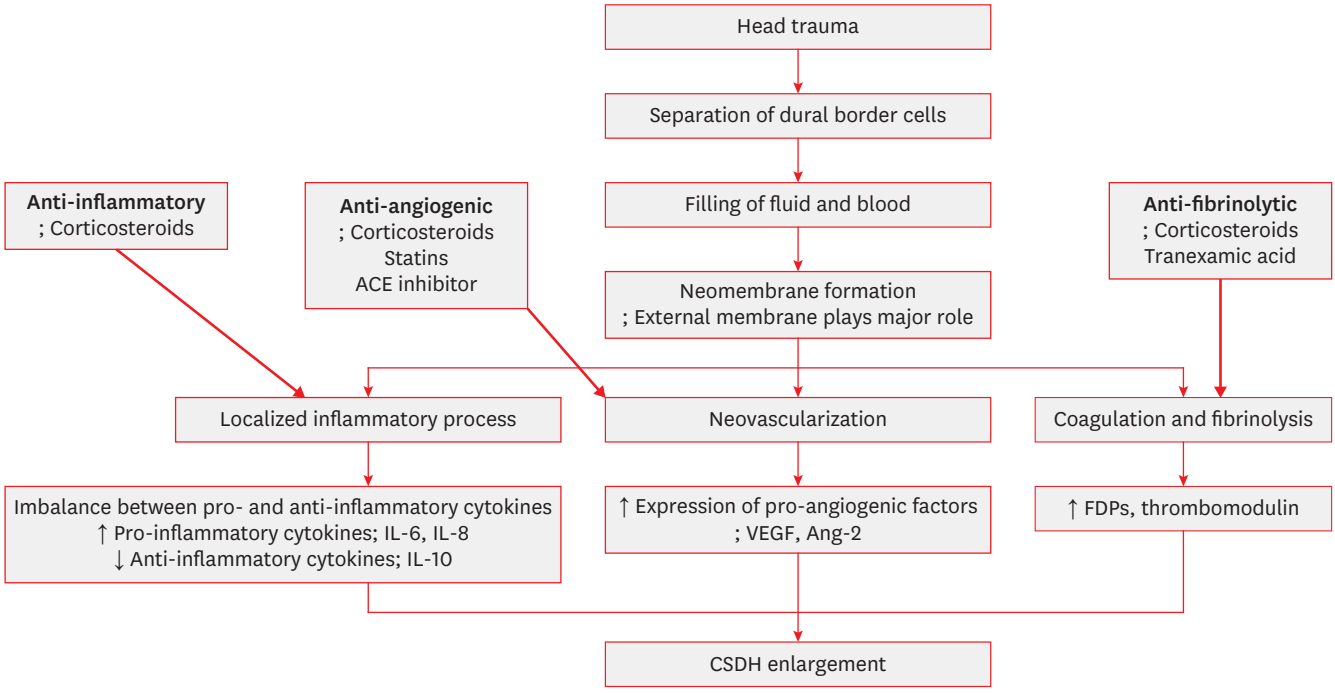

FIGURE 2. Drugs and its targets in the mechanism of chronic subdural hematoma.
ACE: angiotensin converting enzyme, IL: interleukin, VEGF: vascular endothelial growth factor, Ang-2: angiopoietin-2, FDP: fibrinogen degradation product, CSDH: Chronic subdural hematoma.

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and angiotensin converting enzyme (ACE) inhibitors, could be used as a monotherapy or as an adjunct to surgery. In this study, we reviewed representative medical treatments in detail.

CORTICOSTEROIDS

Corticosteroids suppress the synthesis of different pro-inflammatory cytokines, immune system cells, pro-inflammatory enzymes, as well as the production of nitric oxide and cyclooxygenase. Corticosteroids have also been demonstrated to inhibit the expression of VEGF, a powerful inducer of vascular permeability. The rationale of treatment relies on the proven anti-inflammatory, anti-fibrinolytic, and anti-angiogenic effects of corticosteroids.[18]

In a prospective cohort study conducted by Sun et al.[19] in 2005, the results of treating 112 patients with CSDH using dexamethasone were announced. Twenty-six patients were treated with dexamethasone alone, while 69 patients underwent surgical drainage with dexamethasone use. Thirteen patients underwent surgical drainage only, while 4 patients received neither surgery nor dexamethasone use. The outcomes and mortality rates were similar among the group treated with steroids, the group treated with both steroids and surgical drainage, and the group treated with surgical drainage alone. The authors suggest the utilization of dexamethasone as a treatment option for specific patients with CSDH who have a mildly impaired level of consciousness and are not suitable for surgery.

In 2009, Delgado-López et al.[3] conducted a retrospective comparison between a conservative corticosteroid regimen and a surgical regimen involving twist drill craniostomy. The majority of patients treated with dexamethasone (96%) and subdural drain (93%) exhibited favorable outcomes. During hospitalization, adverse events were observed in 34 patients, accounting for 27.8% of the cases. The most frequently encountered adverse events were hyperglycemia (18 patients) and nosocomial infections (11 patients). The authors concluded that, despite considering the limitations of retrospective studies, corticosteroid treatment is not inferior in terms of efficacy, safety, and suitability when compared to surgical treatment.

Berghauser Pont et al.[2] published a retrospective cohort analysis in 2012 on the preoperative corticosteroid treatment in 496 patients with CSDH. In the multivariate analysis, they reported that prolonged administration of dexamethasone prior to surgery is correlated with a reduced rate of CSDH recurrence.

In a prospective study conducted by Thotakura and Marabathina[21] in 2015, the efficacy of steroid treatment was evaluated based on the neurological status changes of 26 patients who received dexamethasone 4 mg every 8 hours for a duration of 3 days. For patients who did not show improvement in symptoms during the three-day treatment period using dexamethasone, surgical burr hole drainage was performed. Patients who showed improvement in symptoms were transitioned to oral steroids with a gradual taper over a span of 4 weeks. The success of steroid treatment was evaluated based on complete symptom recovery and resolution of CSDH observed on computed tomography (CT) scans conducted 6 weeks later. In their study results, they identified four factors that showed a positive correlation: decrease in thickness of the subdural hematoma (SDH), midline shift, density observed in CT scans, and female gender. In conclusion, steroids can play a significant role as part of non-surgical treatment for patients with CSDH, particularly demonstrating beneficial effects in lower grade of patients and female patients.

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In the study by Miah et al.,[12] published in 2023, a noninferiority trial was conducted on symptomatic CSDH patients. They divided the patients into a dexamethasone stand-alone therapy group and a surgery group. However, due to complications and poor outcomes observed in the dexamethasone group, the study was terminated early. Eventually, surgery was performed in 55% of the dexamethasone group. As a result, the study concluded that it could not confirm that dexamethasone therapy is noninferior to surgery when compared to each other.

TRANEXAMIC ACID

TXA is an anti-fibrinolytic medication that works by competitively inhibiting the activation of plasminogen and plasmin activity.[23] Activation of the kallikrein system by plasmin triggers inflammation, resulting in increased vascular permeability and leukocyte migration. This system has been identified in the outer membrane of CSDH. Thus, there is a hypothesis that TXA may inhibit hyperfibrinolytic activity and the associated increased vascular permeability in CSDH. This inhibition could potentially contribute to the gradual absorption of the hematoma.[18]

The first use of TXA in the treatment of CSDH was reported in a case report in 2000. In that case report, a hemodialyzed patient with recurrent CSDH even after three surgical treatments was given TXA which resulted in complete radiological resolution of CSDH.[22]

In a retrospective study conducted by Kageyama et al.[9] in 2013, TXA treatment was administered to 21 patients with CSDH. Among the 21 patients, 18 patients underwent TXA treatment without surgical intervention, and complete resolution of the hematoma was observed after treatment.

Another study in 2016 reported that bedside twist drill evacuation was performed on 20 CSDH cases in 14 patients, followed by oral TXA treatment and resulted in 95% reduction in the initial SDH volume. Furthermore, during the treatment period with TXA, no increase in residual SDH was observed, and during the follow-up period after discharge, no additional procedures were required.[20]

In 2022, A study was conducted on patients who underwent single burr hole drainage, involving a total of 240 individuals, to investigate the effects of adjunctive TXA on the resolution and recurrence of CSDH. In this study, the 240 patients were classified into three groups: TXA, non-TXA, and antithrombotic (AT). The primary outcome was the recurrence of CSDH, while resolution was set as the secondary outcome. The recurrence rate was found to be the lowest in the TXA group at 2.4%, but there was no statistical significance observed. CSDH resolution rates did not differ statistically significantly among the three patient groups, but TXA administration was associated with CSDH resolution in the multivariate analysis. And, the median estimated time to resolution was significantly shorter in the TXA group (51 days in TXA group, 109 days in non-TXA group, and 88 days in AT group). The researchers concluded that utilizing TXA as an adjunctive treatment after burr hole drainage is effective in achieving resolution of CSDH by promoting faster reduction of hematoma. Additionally, TXA may have a beneficial impact on reducing the likelihood of recurrence.[28]

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STATIN

Atorvastatin acts as a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. It enhances the uptake of low-density lipoprotein (LDL) by increasing the expression of LDL receptors on the hepatic cells and mononuclear cells, and helps reduce the levels of circulating LDL-cholesterol particles.[7]

In a study using a rat model, in 2016, it was observed that low-dose atorvastatin reduced the volume of SDH (subdural hematoma) and neurological deficits. In accordance with these results, the administration of a low dose of atorvastatin demonstrated an upregulation of angiopoietin-1 and VEGF expression in the connective tissue of the SDH wall. As a result, there was an observed increase in vascular density and enhanced vascular maturation.[24]

In a double-blind, randomized, placebo-controlled trial in 2018 conducted on 200 patients, a dose of 20mg of atorvastatin was administered for 8 weeks. The results revealed a significant reduction in hematoma volume after the 8-week treatment period. The researchers concluded that the administration of atorvastatin is safe, efficient, and cost-effective as a non-surgical treatment for CSDH. They particularly noted its effectiveness in patients aged 65 and older, as well as those with a hematoma volume of 30 mL or more.[8]

In a study conducted in 2016 by Xu et al.,[26] 109 patients were divided into three groups to assess the effects of atorvastatin. The patients were categorized into a conservative treatment group receiving atorvastatin, a surgical treatment group with or without atorvastatin use. In their study findings, the group of patients who received conservative treatment with atorvastatin showed a significant reduction in hematoma volume. On the other hand, atorvastatin did not statistically significantly reduce hematoma volume in patients undergoing surgical treatment. However, in the follow-up results that assessed hematoma volume and neurological status three months later, the group of patients who underwent surgical treatment and received atorvastatin showed significant improvement compared to the group of patients who did not receive atorvastatin.

Klein et al.[10] investigated the potential of statins to reduce the rate of repeat surgery after initial evacuation of CSDH in 2021. The study was carried out involving 407 patients, who were categorized into two factions depending on whether they were being treated with statins or not. According to the findings, the incidence of additional surgeries was not decreased by the use of statins.

ANGIOTENSIN CONVERTING ENZYME INHIBITOR

ACE inhibitors are widely recognized pharmaceutical compounds utilized for managing arterial hypertension. Studies have demonstrated their effectiveness in inhibiting the formation of new blood vessels in the retinas of diabetic patients.[7] Taking into account the angiogenic hypothesis of CSDH, it is plausible to hypothesize that prolonged use of ACE inhibitors could potentially have beneficial effects on the progression of CSDH and postoperative outcomes.[4,6,7]

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In a study conducted by Weigel et al.[25] with 310 patients in 2017, it was found that the recurrence rate was statistically significantly lower in the group of patients who were taking ACE inhibitors compared to the group of patients who were not taking (5% vs. 18%).

However, in a prospective randomized controlled study conducted by Poulsen et al.[15], in 2014, it was found that ACE inhibitors did not reduce the size of residual CSDH nor decrease the recurrence rate of CSDH following burr hole surgery. In another retrospective case-control study conducted on 203 patients, it was actually observed that the group of patients who were administered ACE inhibitors exhibited higher hematoma volume and a higher frequency of recurrence. Their hypothesis suggests that the elevated hematoma volume and the higher frequency of recurrence observed in patients taking ACE inhibitors may be attributed to the ACE inhibitor-induced elevation of bradykinin. This elevation could lead to increased vascular permeability of the neomembranes, which are highly vascularized in CSDH.[14]

CONCLUSION

The natural history and pathogenesis of CSDH have not been clearly elucidated to date, and surgical treatment remains the gold standard. As a result, various medications are currently being used for medical treatment of CSDH, but the evidence is limited. However, if additional research on the pathogenesis of CSDH is conducted and randomized controlled trials of pharmacological treatment involving a large number of patients are carried out in the future, it appears that pharmacological treatment could be sufficiently utilized in elderly patients or patients who are unable to undergo surgical treatment.

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