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EDITORIAL

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Exploring the treatment of Chronic Subdural Hematoma: Crossing the river by feeling the stones

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Chronic subdural hematoma (CSDH) is a common disease in neurosurgery and is projected to become the most prevalent neurosurgical disease by 2030 as the ageing population and increased use of anticoagulants. The pathophysiological mechanisms of CSDH remain unclear, and multiple drivers promote the recurrence and progression of CSDH, including inflammation, membrane formation, angiogenesis and fibrinolysis, which are interrelated, constituting a complex mechanism. Surgical treatment is currently the predominantly clinical option, including surgical drainage, burr hole drainage, or craniotomy with endoscopic assistance. Because most CSDH patients are elderly, several are unsuitable for surgical treatment. Clinical researchers are, therefore, continuously exploring enhanced treatment strategies in addition to surgical treatment (Figure 1). For instance, Jiang, R et al. conducted a multicenter, randomized, placebo-controlled, double-blind phase II clinical trial demonstrating that atorvastatin may be a safe and effective non-surgical alternative therapy for patients with CSDH.[1] Ishita P Miah et al. conducted a multicenter, open-label, controlled, noninferiority trial comparing the effects of dexamethasone with surgical treatment, showing that dexamethasone was less effective than surgical treatment.[2]

The recurrence or progression rate of symptomatic chronic subdural hematoma remains high after standard treatment. This may be due to the repeated hemorrhage from neovascularization in the subdural area, which is supplied by the middle meningeal artery. Based on this, intravascular embolization of the middle meningeal artery is a promising therapeutic approach to reduce hematoma growth and recurrence of CSDH. Recently, the New England Journal of Medicine (NEJM) published three randomized controlled trials (EMBOLISE,[3] MAGIC-MT,[4] and STEM[5]) evaluating the efficacy and safety of middle meningeal artery embolization(MMAE) plus standard treatment versus standard treatment alone among nonacute subdural hematoma patients. The EMBOLISE trial included 400 patients, with 197 patients randomly assigned to the treatment group. Results only showed a numerical trend toward reduced risk of reoperation for recurrence or progression within 90 days with middle meningeal artery embolization plus surgery

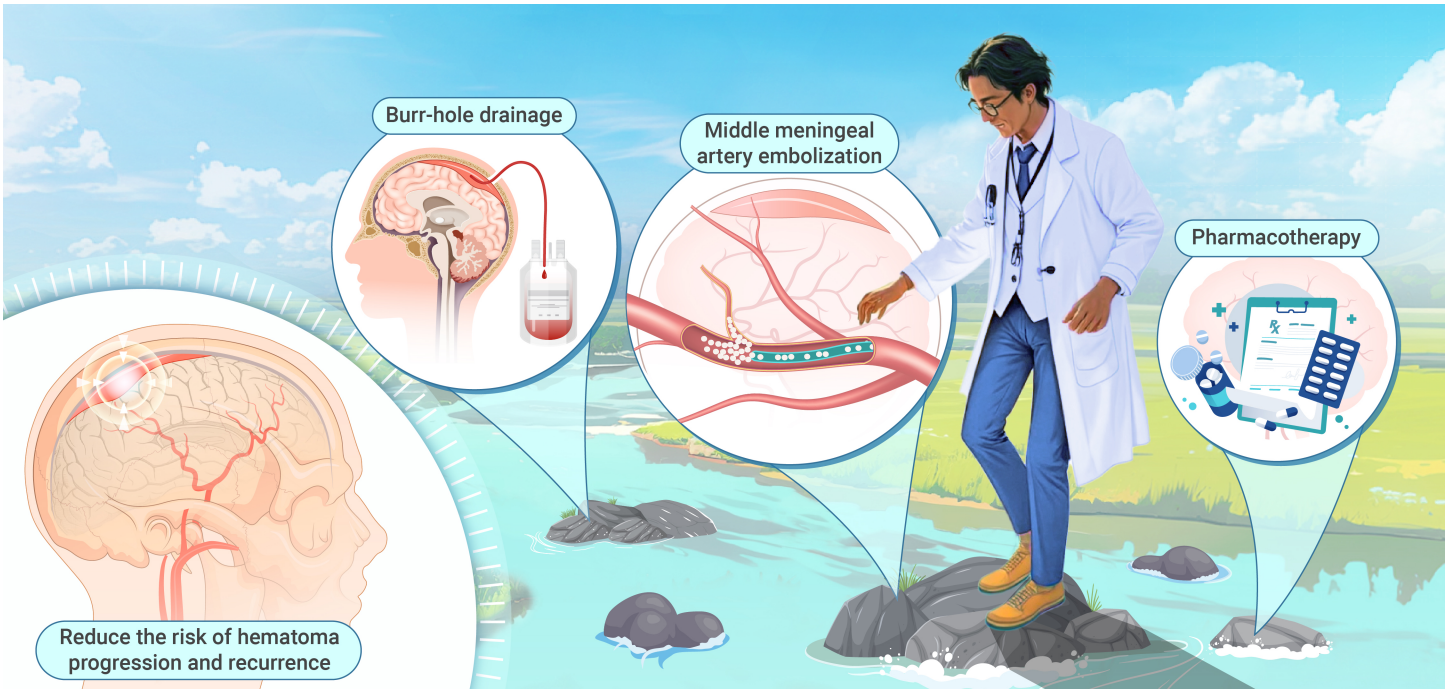

Figure 1. Exploring the treatment of Chronic Subdural Hematoma: Crossing the river by feeling the stones Current therapeutic strategies for chronic subdural hematoma: burr-hole drainage, middle meningeal artery embolization and pharmacotherapy.

compared to surgery alone (4.1% vs. 11.3%, P=0.08). Regarding safety, the 90-day mortality rate in the treatment group was slightly higher than in the control group (5.1% vs. 3.0%, P=0.32), though this difference was not statistically significant. Besides, the loss to follow-up was substantial (13.2% of the patients), and sample attrition may have led to inaccurate results because patients who were lost to follow-up may have differed in their condition and response to treatment from those who completed follow-up. The MAGIC-MT trial included 722 patients, with 360 patients randomly assigned to the embolization group. Results indicated that the 90-day recurrence or progression rate of symptoms with middle meningeal artery embolization was similar to conventional treatment (6.7% vs. 9.9%, P=0.10), and the rate of serious adverse events in the embolization group was lower than in the standard treatment group (6.7% vs. 11.6%, P=0.02). While the MAGIC-MT trial did not show a significant advantage in terms of recurrence rate, the reduction in serious adverse events in the embolization group is promising, though it warrants further exploration. Notably, the reported recurrence rate in the MAGIC-MT(4.7-5.2%) was substantially lower than historical estimates of 9.3~27.5%,[4] raising concerns about potential selection bias toward low-risk patients. The STEM trial included 310 patients, with 149 randomly assigned to the embolization group. At 180 days, the composite outcome was assessed (recurrence or residual hematoma, reoperation or rescue surgery, or severe disabling stroke, myocardial infarction, or death due to neurological

reasons), showing a significantly lower risk of composite outcome events in the embolization group compared to the control group (16% vs. 36%, P=0.001). Within 180 days, 12 patients in the embolization group (8%) and 9 patients in the control group (5%) died. The STEM trial also has some limitations. Data were missing for 15% of the patients in the intention-to-treat population, which may affect the accuracy of the results. Although neurogenic deaths had lower values in the embolized group, overall mortality had higher values in the embolized group (8% vs. 5%), which requires further studies to clarify the causes and potential risks. The three trials differed slightly in definitions of standard treatment, ethnic differences and embolization materials (EMBOLISE and MAGIC-MT used the Onyx liquid embolic system, while STEM used the nonadhesive liquid embolic agent Squid). Summarizing the three trials, we think there are three points of concern. First, the number needed to treat (NNT) varied drastically between EMBOLISE (NNT=14) and STEM (NNT=200), suggesting that MMAE's benefit may be confined to specific subgroups not yet clearly defined. Second, while the EMBOLISE and MAGIC-MT trials assessed outcomes at 90 days (the reported incidence of recurrence or progression with control group: 11.3% and 9.9%, respectively), STEM's 180-day follow-up revealed a 36% composite event rate in controls. This disparity cannot be fully attributed to extended observation alone, implying fundamental differences in patient selection or endpoint definitions. Third, given that asymptomatic/minimally symptomatic CSDH often resolves spontaneously, what is the benefit of performing MMAE in patients who do not require surgical treatment (burr-hole drainage)?

Overall, middle meningeal artery embolization as an adjunct to standard treatment for symptomatic non-acute subdural hematomas may be more beneficial in preventing recurrence and progression compared to standard treatment. However, all three trials were conducted during the coronavirus disease pandemic, which not only resulted in a few lost cases but also did not exclude the lethal effect of coronavirus itself on elderly patients. The available studies did not assess the long-term impact of embolization on patients, such as changes in quality of life, functional recovery, and cognitive functioning, which are essential for a comprehensive assessment of treatment outcomes. Larger, more rigorous and comprehensive trials are needed to validate the optimal timing of embolization further, patient selection criteria for maximum therapeutic benefit, optimal embolic agent selection, and refined treatment techniques. Finally, existing studies have not delved into the underlying mechanisms of hematoma recurrence, such as angiogenesis and inflammatory responses in the hematoma membrane and the effect of embolization therapy on these mechanisms. More effective therapeutic strategies can be developed through a clearer understanding of the pathophysiological process. Further exploration of CSDH is needed, both in terms of pathophysiological mechanisms and clinical management.

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DECLARATION OF INTERESTS

The authors declare no competing interests.