Review

Perioperative Management in Aneurysmal Subarachnoid Hemorrhage; Focus on the Prevention of Delayed Cerebral Ischemia

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Perioperative Management in Aneurysmal Subarachnoid Hemorrhage; Focus on the Prevention of Delayed Cerebral Ischemia

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Abstract: Background: Aneurysmal subarachnoid hemorrhage (aSAH) remains a life-threatening cerebrovascular event with high rates of mortality and long-term morbidity. Among its complications, delayed cerebral ischemia (DCI) is a major contributor to poor clinical outcomes. Although cerebral vasospasm has traditionally been considered the primary mechanism underlying DCI, recent studies have revealed the multifactorial nature of this condition. **Objective:** This review aims to provide a comprehensive overview of the pathophysiology, preventive strategies, and current treatment options for DCI following aSAH. **Methods:** We performed a narrative review of the literature, focusing on recent findings regarding the etiologies of DCI—including cerebral vasospasm, microvascular spasm, microthrombi, and cortical spreading depolarization—and the effectiveness of various prophylactic and therapeutic interventions. **Results:** Emerging evidence highlights that vasospasm alone does not account for all cases of DCI. Pharmacological approaches such as nimodipine, clazosentan, and fasudil have shown varying degrees of efficacy. Circulatory management and removal of subarachnoid hematoma via CSF drainage or thrombolytics may reduce DCI risk, although their impact on long-term neurological outcomes remains controversial. Endovascular therapy and adjunctive agents such as cilostazol or anticoagulants have demonstrated potential but require further validation through large-scale trials. **Conclusions:** Effective DCI prevention and treatment require a multimodal approach targeting diverse pathological mechanisms beyond vasospasm. Improved risk stratification, early detection, and individualized therapy are essential for advancing the management of patients with aSAH.

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Introduction

Globally, stroke ranks as the second leading cause of death and disability-adjusted life-years [1]. Intracranial aneurysm rupture, causing aneurysmal subarachnoid hemorrhage (aSAH), accounts for 5% of all strokes [2,3]. The early mortality rate post-SAH exceeds 30%, and most survivors endure long-term disabilities or cognitive complications [2,4]. Cerebral vasospasm affects approximately 70% of aSAH patients, typically manifesting between days 7 and 10 post-bleed [5–7]. Delayed cerebral ischemia (DCI), a complex ischemic complication of aSAH, occurs in 17-40% of these patients and is associated with poorer clinical outcomes [8–11]. Historically, cerebral vasospasm that went unrecognized or was inadequately treated was often cited as a primary cause of mortality in autopsies following aSAH [12]. However, the pathogenesis of DCI extends beyond simple vasospasm, encompassing a spectrum of factors such as disruption of the blood-brain barrier, microthromboses, cortical spreading depolarizations, and the breakdown of cerebral autoregulation [13]. Interventions that focus solely on vasospasm have demonstrated limited success in ameliorating DCI or reducing the death rate among aSAH patients. Therefore, honing risk stratification methods, improving

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prophylaxis, and early detection and management of DCI are essential in advancing the treatment of aSAH.

Today, various pharmacological strategies aimed at reducing mortality and DCI while enhancing neurological and functional recovery post-aSAH have been reported. In this review, we summarized the etiology and treatment of post-aSAH DCI.

The Etiology of DCI

(1) Cerebral Vasospasm and Subarachnoid Hematoma

The volume and distribution of subarachnoid hematomas are considered risks for cerebral vasospasm [14]. In animal models, it has been reported that oxyhemoglobin contained in the subarachnoid hematoma can induce vasospasm, while methemoglobin and bilirubin do not significantly cause vasospasm [15–17]. The mechanism by which oxyhemoglobin induces cerebral vasospasm may involve the release of reactive oxygen species during its oxidation to methemoglobin, decreased production of PGI2, and increased production of PGE2 [18]. There are no specific interventions, but draining the subarachnoid space to remove the blood breakdown products may be a sensible approach.

(2) Microvascular Spasm

There may be discrepancies between imaging findings of cerebral vasospasm and clinical symptoms, suggesting the involvement of microvascular spasm that is not detectable by imaging. Studies using PET-CT to assess cerebral blood flow and cerebral blood volume have shown that unlike cases of carotid occlusion, patients with cerebral vasospasm following SAH do not exhibit peripheral vascular dilation due to autoregulation [19]. In SAH models with blood injected into the cerebral ventricles, narrowing of the microvessels within the brain parenchyma has been observed, suggesting microvascular spasm [20]. Microvascular spasms can occur within 24 hours of SAH onset and pose a risk for subsequent cerebral vasospasm [21].

(3) Microthrombi

In autopsies of SAH patients (n=29), a more significant number of microthrombi were found in those who developed DCI, suggesting microthrombi as one of the pathological states related to DCI [22]. Furthermore, observational studies following blood markers after SAH onset reported that levels of von Willebrand factor rise within 72 hours of onset, and platelet-activating factor increases within four days of SAH, continuing to rise to 14 days [23,24]. There is a correlation between the volume of subarachnoid hematoma and increased coagulation activity, and several observational studies have reported a potential link between enhanced coagulation function and DCI [23,25–27].

(4) Cortical Spreading Depolarization (CSD)

CSD involves a sustained propagation of neuronal depolarization across the cerebral cortex at speeds of 2-6 mm/min and is associated with cerebral edema. It is also considered a neuroprotective response, inducing contraction and dilation in brain vessels. While CSD is typically not problematic in an undamaged brain, it is observed in 70-80% of severe SAH patients, and recurring CSD episodes in a damaged brain can worsen cerebral ischemia, even in the absence of cerebral vasospasm [28–30].

The Prevention and Treatment of DCI

Over the past 60 years, various preventative and therapeutic measures against cerebral vasospasm have been explored, yet more established methods still need to be determined [31,32]. As previously mentioned, various causes contribute to Delayed Cerebral Ischemia (DCI), and approaches to address these have been examined, mainly through randomized controlled trials (RCTs).

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(1) Circulatory Management

Following SAH, conditions such as central salt wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) can lead to hyponatremia and reduced circulating blood volume, which increases the risk of DCI [33]. In cases of SIADH, restriction of free water intake is commonly practiced, which, however, might increase the risk of cerebral ischemia [34]. In post-SAH patients, isotonic fluids are typically used to manage circulation, prevent hyponatremia, and reduce circulating blood volume. Previously, the Triple-H therapy, which involved induced hypertension, hypervolemia, and hemodilution, was practiced but failed to demonstrate efficacy [35]. Some observational studies have associated positive fluid balance after SAH with poor outcomes, and the latest guidelines documented managing infusion to maintain euvolemia [36–38]. Complications like neurogenic pulmonary edema and Takotsubo cardiomyopathy can make circulatory management more challenging.

After the onset of DCI, if there are no signs of fluid overload, fluid loading is first performed to see if it improves neurological outcomes (CBF responsiveness to infusion) [39]. Once the circulating blood volume is optimized, if there are no concerns like untreated aneurysms, the target blood pressure is set higher, and vasoconstrictors are administered. Reports suggest these management strategies improve neurological outcomes in about 70% of DCI cases [40].

(2) Removal of Subarachnoid Hematoma

The presence of a subarachnoid hematoma is considered a risk factor for cerebral vasospasm, and its removal through drainage is an anticipated, albeit invasive, intervention method. Various techniques, such as ventricular drainage, lumbar drainage, and intrathecal administration of thrombolytic agents, have been considered, but most studies are observational. An RCT dividing 210 SAH patients into two groups based on the presence or absence of lumbar drainage showed a decreased DCI. However, there was no significant difference in neurological outcomes after six months [41]. Furthermore, the majority of patients in this study had mild symptoms, and the effectiveness of this intervention for moderate to severe SAH remains unclear.

A meta-analysis of five RCTs considering intrathecal administration of thrombolytic agents in 465 SAH patients reported improvements in cerebral vasospasm, DCI, and neurological outcomes [42]. However, excluding the RCT that combined this treatment with intrathecal nimodipine, no statistically significant differences were observed, indicating that this treatment has yet to be established as standard.

(3) Endovascular Treatment

Endovascular treatment is divided into mechanical dilation using a balloon and intra-arterial administration of vasodilatory drugs. It is considered for patients whose medical treatment is ineffective or poses a high risk of complications. An RCT evaluating prophylactic percutaneous transluminal cerebral balloon angioplasty (PTCBA) within 96 hours of SAH onset in patients at high risk of DCI due to large subarachnoid hematomas showed no difference in the occurrence of DCI or neurological outcomes, suggesting that preventive PTCBA is not recommended [43]. Additionally, complications related to PTCBA included arterial perforation in four cases, three of which were fatal. No RCTs have been reported regarding endovascular treatments as interventions for DCI. Observational studies have shown them effective in over 90% of cases, but approximately 20% required retreatment due to symptom recurrence [44]. Endovascular treatment should also be conducted earlier after the onset of DCI [45]. Vasodilatory drugs used intra-arterially include verapamil, nicardipine, nimodipine, and fasudil [46].

(4) Calcium Channel Blockers

Nimodipine, a dihydropyridine calcium channel blocker, is sanctioned by the US Food and Drug Administration for neurological improvement for post-aSAH patients. A Cochrane review assessing

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treatments involving calcium channel blockers, including their combinations, comprising 16 RCTs with 3,661 participants, showed that these drugs improved neurological outcomes [47]. However, stratified analyses revealed that while oral nimodipine exhibited similar beneficial effects, intravenous nimodipine and other calcium channel blockers did not improve outcomes. RCTs reporting a reduction in DCI with oral nimodipine did not show a decrease in cerebral vasospasm [48]; thus, other neuroprotective actions such as microvascular dilation, reduction in platelet aggregation, and decreased calcium-dependent excitotoxicity are considered. Similar findings have been reported for nicardipine, another L-type dihydropyridine calcium channel blocker. High-dose continuous nicardipine administration (0.15 mg/kg/hr) reduced cerebral vasospasm [49], but there was no difference in neurological outcomes after three months, potentially due to hypotension affecting cerebral perfusion. An RCT comparing low-dose (0.075 mg/kg/hr) with high-dose (0.15 mg/kg/hr) nicardipine found no difference in DCI incidence (~31%) or neurological outcomes after three months in both groups, and more adverse events led to early termination in the high-dose group [50].

(5) Clazosentan

Previous studies have suggested that endothelin-1, a potent and persistent endogenous vasoconstrictor, plays a role in the development of cerebral vasospasm [51]. After aSAH onset, the concentration of endothelin increases in the cerebral arteries, thereby increasing the sensitivity to endothelin-1 and intracellular calcium concentration [52].

Clazosentan, a selective endothelin receptor antagonist, inhibits endothelin-mediated cerebral vasospasm [53]. Several trials have evaluated the efficacy and safety of clazosentan for preventing or modulating cerebral vasospasm in patients with aSAH [54–58]. Clazosentan was recently assessed in placebo-controlled, randomized, double-blind studies in adult Japanese patients with aSAH and showed a significant reduction in cerebral vasospasm-related morbidity and all-cause mortality within six weeks post-aSAH [59]. In real-world data analysis, clazosentan effectively significantly reduced the combined incidence of vasospasm-related morbidity and all-cause mortality in the case of aSAH [60,61]. Clazosentan has only been available in actual clinical use for about three years in Japan, and further evidence needs to be established in the future.

(6) Fasudil Hydrochloride

Fasudil hydrochloride, a Rho kinase inhibitor, exerts vasodilatory effects by antagonizing intracellular calcium ions and myosin light chain and is involved in processes such as vasoconstriction, activation of inflammatory cells, and endothelial cell damage. An RCT comparing fasudil with placebo over 14 days in post-SAH patients showed decreased DCI and improved neurological outcomes after one month [62]. Another RCT comparing oral nimodipine as a control showed no difference in DCI but improved neurological outcomes after one month [63]. A meta-analysis of eight such RCTs reported similar results, although the sample sizes were generally small, indicating a need for larger-scale RCTs to substantiate these findings [64].

(7) Antiplatelet and Anticoagulant Drugs

A 2007 Cochrane Review examining the efficacy of antiplatelet drugs in SAH patients (7 RCTs, n=1,385) found no significant differences in delayed cerebral ischemia (DCI), neurological outcomes, or hemorrhagic complications [65]. Furthermore, although several observational studies have reported on the effectiveness of dual antiplatelet therapy (DAPT), results are inconsistent, and there is a suggested risk of increased bleeding [66,67].

Cilostazol, a phosphodiesterase inhibitor, possesses antiplatelet, endothelial protective, and vasodilatory effects. Several RCTs have reported improvements in cerebral vasospasm, DCI, and neurological outcomes with cilostazol, though the sample sizes were small, indicating a need for verification through larger-scale studies [68–70].

 doi:10.20944/preprints202503.2412.v1

Regarding anticoagulant therapy, two RCTs comparing low molecular weight heparin subcutaneous injections with placebo reported reductions in DCI and stroke but no difference in neurological outcomes after three months [71,72]. Continuous infusion of heparin has been observed in studies to improve DCI, stroke, and cognitive function after three months [73–75].

(8) Statins

Statins are anticipated to have anti-inflammatory, vasodilatory, and antithrombotic effects. A meta-analysis of six randomized trials on statin therapy for aSAH revealed a decrease in vasospasm without significant improvement in DCI or mortality [76]. One hypothesis is that extended statin dosing may increase the risk of bacteremia within this patient group, neutralizing any vasospasm mitigation benefits [77]. Research efforts are pivoting towards examining shorter-duration and combination statin therapies [78]. Given that existing dosing regimens have not yielded outcome benefits, routine statin use for aSAH patients is not currently advised [79].

(9) Magnesium

Although preclinical studies posited that magnesium sulfate could augment cerebral blood flow and curtail vasospasm [80], clinical evidence has not demonstrated outcome benefits with its intravenous administration [81]. There is ongoing debate regarding the significance of magnesium concentration within the cerebrospinal fluid over peripheral levels, a theory yet to be empirically substantiated. Based on present data, magnesium sulfate is not endorsed for routine use to enhance neurological outcomes post-aSAH [82].

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