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REVIEW ARTICLE

Therapeutic small molecules in the development of treatment for subarachnoid hemorrhage

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Abstract

Subarachnoid hemorrhage (SAH) is a severe and often fatal condition characterized by the accumulation of blood beneath the arachnoid layer of the meninges. Predominantly affecting individuals in the 40–60 age range, it is commonly caused by head trauma from falls or car accidents. Ruptures of cerebral aneurysms also contribute significantly to SAH. Risk factors for SAH include hypertension and smoking, and symptoms typically include severe headache and neck pain. Diagnosing SAH typically involves a combination of medical history, physical examination, and imaging studies such as computed tomography angiography or magnetic resonance imaging angiography. Recent research suggests that pharmaceutical management of intracerebral hemorrhage (ICH) includes the administration of recombinant activated factor VII, tranexamic acid, and aggressive blood pressure reduction. For patients with significant SAH and ICH, minimally invasive surgical procedures for hematoma evacuation, as well as surgical evacuation of SAH and ICH, have proven to be highly beneficial. Furthermore, an emerging area of treatment involves therapeutic small molecules designed to interrupt the pathophysiological pathways leading to SAH. This novel approach holds promise for advancing our understanding and management of this complex medical condition.

Keywords: Subarachnoid hemorrhage; Neurosurgery; Therapeutic small molecules; Novel therapy; Pharmacological management

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1. Introduction

Subarachnoid hemorrhage (SAH) remains a significant contributor to both long-term morbidity and mortality. This review employs a variety of research articles to guide readers through the pathophysiology, risk factors, diagnosis, and treatment options for SAH. Of particular interest are the innovative therapeutics currently under exploration for SAH. Future directions in SAH, as well as controversial issues, current advancements, and prognostic factors, are comprehensively addressed.

The treatment of SAH can be approached on an individualized basis, incorporating combinations of newer therapies alongside previously available surgical or medical options tailored to address the specific needs of each patient. The selection of specific interventions

for individual patients may contribute to a reduction in the occurrence of complications and facilitate targeted treatments. This approach provides future researchers the opportunity to explore these novel therapies, aiming to manage diverse patient types with unique combinations tailored to the specific needs of each individual. Subsequently, this research can contribute to the development of an updated guideline for reference in the future.

The major limitation of this review lies in its inability to evaluate the combinations of novel therapies along with the currently available traditional therapies. The principal objective of this article is to furnish comprehensive information regarding the current treatment options for SAH, placing particular emphasis on the discovery and ongoing research of novel therapies. Another objective is to provide researchers with a further direction for evaluating the efficacy of these therapies, especially when used in combination with traditional therapy options.

This review was formulated based on the results of searches conducted on PubMed, Embase, Scopus, and conference abstracts up to the year 2023 for studies related to SAH and its treatment. The study adheres to the PRISMA guidelines for systematic review. Information was systematically retrieved from the aforementioned databases, and relevant studies were identified based on the crucial information they provided. Each article's information was thoroughly reviewed and extracted to construct a comprehensive database. This approach ensured that the authors had access to all pertinent information during the writing process of this review article, thereby minimizing the risk of overlooking important details.

1.1. Understanding SAH

Blood can infiltrate the cerebrospinal fluid due to cerebral insult, a burst intracranial aneurysm, and/or other severe head trauma, frequently resulting in a deadly condition known as SAH[1,2]. Failure to restore normal blood flow can result in fatal consequences, including death, hydrocephalus, stroke, and permanent disability. SAH, a form of cerebrovascular disease, is recognized as one of the most severe and fatal neurological emergencies[3]. It is estimated that up to 50% of patients experiencing SAH succumb within 30 days of onset, with an additional 30% suffering from moderate-to-severe morbidity[4-8].

1.2. Causes and risk factors of SAH

Ruptures of pre-existing intracranial aneurysms are the primary cause of SAH, affecting 1% to 5% of the general population[3,9]. In addition, other causes, such as cerebrovascular malformations, vascular abnormalities at the skull base, and head trauma, can also precipitate SAH[10-12]. Notably, spinal vascular pathologies and isolated spinal artery aneurysms are also identified as potential causes[13]. Risk factors associated with SAH include hypertension and smoking[14]. Symptoms commonly associated with SAH include severe headache, neck pain, nausea or vomiting, and photophobia[15]. In some cases, SAH may present with atypical symptoms such as back pain and lower-extremity weakness. Complications of SAH that may result in death include hemorrhage, cerebral edema, infection, pneumonia, external ventricular shunt, and ischemic damage[16-18]. A comprehensive understanding of the causes and risk factors of SAH is important for its prevention, diagnosis, and effective treatment.

1.3. Symptoms and diagnosis of SAH

Symptoms of SAH vary depending on the severity and location of the bleeding[19]. Common symptoms include sudden and severe headaches, neck pain or stiffness, nausea and vomiting, sensitivity to light (photophobia), changes in vision or double vision, seizures, and loss of consciousness[20-22]. The diagnosis of SAH typically involves a combination of medical history, physical examination, and imaging studies such as computed tomography angiography or magnetic resonance imaging angiography[23,24]. The pathophysiological mechanisms and symptoms of SAH are illustrated in Figure 1.

2. Pathophysiology of SAH

SAH is a complex and life-threatening condition characterized by blood infiltration into the subarachnoid space surrounding the brain. The pathophysiology of SAH involves a series of events that lead to both immediate and delayed complications. The following subsections provide a comprehensive overview that integrates findings from multiple references.

2.1. Rupture of intracranial aneurysm

The rupture of an intracranial aneurysm plays a pivotal role in the pathophysiology of SAH. When considering the pathogenesis of SAH, consulting these key sources yields valuable insights. Osgood[25] discusses the complex pathophysiology of aneurysmal SAH, highlighting the significance of aneurysmal rupture as the primary trigger for this devastating condition. Boling and Groves[26] delve into the management of SAH, emphasizing that the rupture of intracranial aneurysms leads to the sudden release of blood into the subarachnoid space. D'Souza[27] provides a comprehensive perspective on aneurysmal SAH, underlining how the rupture of an intracranial aneurysm disrupts the normal cerebral environment and initiates a cascade of events.

Furthermore, Sorrentino *et al.*[28] contribute a contemporary narrative review that specifically addresses

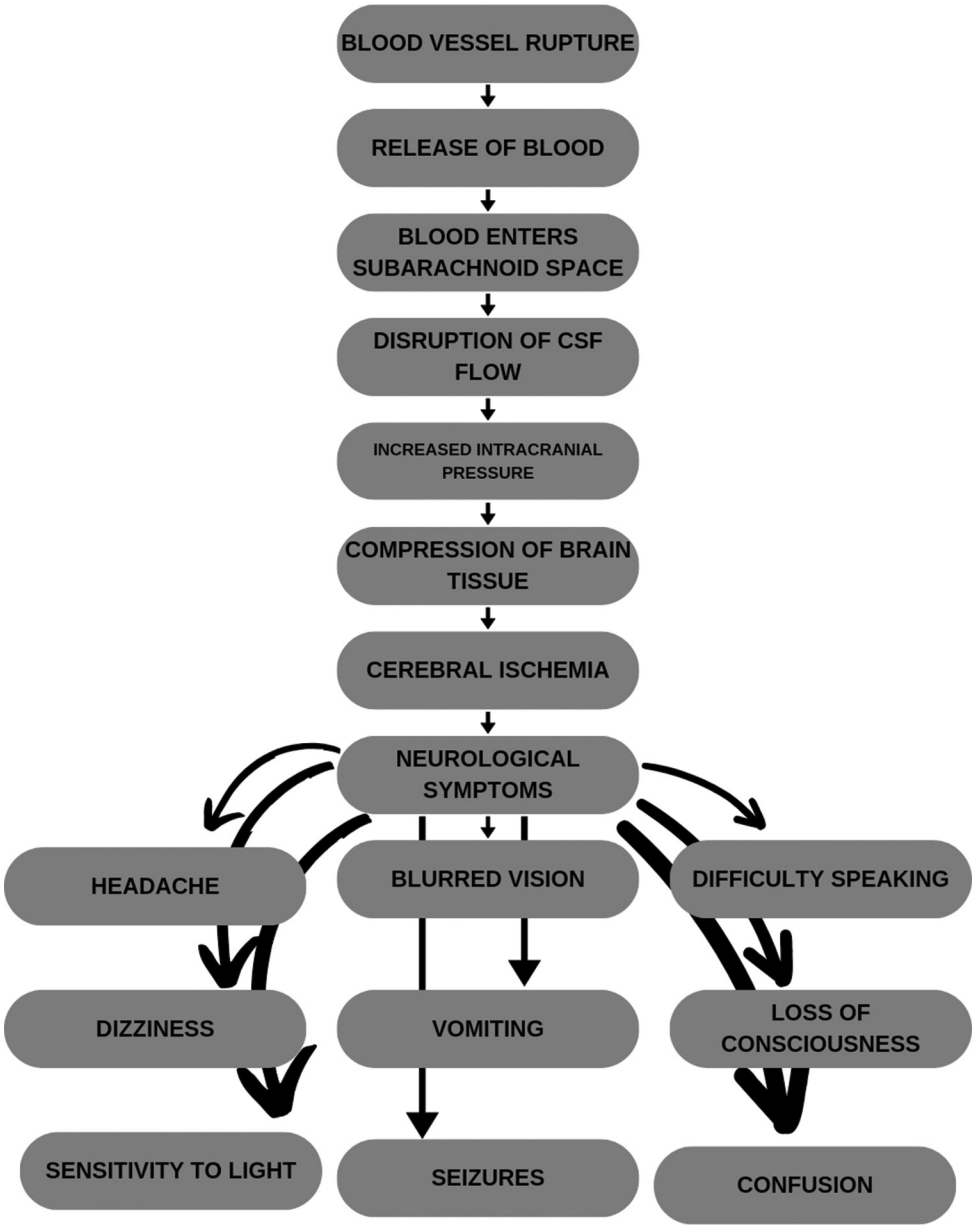


Figure 1. Pathophysiology and symptoms of subarachnoid hemorrhage.

the persistence of headaches following aneurysmal SAH, shedding light on the long-term consequences of aneurysmal rupture. Collectively, these sources underscore the critical role of intracranial aneurysm rupture in the pathophysiology of SAH. This highlights the need for early diagnosis and intervention to mitigate the potentially severe consequences associated with this event.

2.2. Toxic hemoglobin products

The breakdown of hemoglobin results in the production of toxic substances, leading to the following adverse effects:

(i) Oxidative stress: Hemoglobin breakdown releases heme, which generates reactive oxygen species (ROS). These ROS induce oxidative stress, damaging neuronal and vascular structures. Oxidative stress is associated with cerebral vasospasm, delayed cerebral ischemia (DCI), and brain injury following SAH. Sorrentino *et al.*[28] discuss the persistence of headaches after SAH, attributing them, in part, to the oxidative stress and inflammation resulting from toxic hemoglobin products.

(ii) Inflammation: Toxic hemoglobin products can trigger an inflammatory response within the subarachnoid space and brain parenchyma. This inflammation,

mediated by cytokines and immune cells, can exacerbate tissue damage.

(iii) Vasoconstriction: Hemoglobin and its degradation products, such as bilirubin, can induce vasoconstriction and impair cerebral blood flow regulation. This can result in complications like cerebral vasospasm, which is associated with poor outcomes in SAH patients. Towner *et al.*[29] discuss the use of mechanical ventilation in aneurysmal SAH, potentially touching upon the role of vasoconstriction in the context of ventilatory support.

2.3. Blood in subarachnoid space

Voldby[30] conducted a literature review highlighting the relationship between SAH and cerebral vasospasm. They emphasize that the initial insult, characterized by the presence of blood in the subarachnoid space due to aneurysmal rupture or other causes, triggers a cascade of events leading to vasospasm. The presence of blood components, particularly hemoglobin breakdown products, contributes to inflammation and dysfunction of cerebral blood vessels, ultimately resulting in vasospasm – a hallmark complication of SAH.

Voldby[30] provides insights into the pathophysiology of SAH based on both experimental and clinical data. The presence of blood in the subarachnoid space is identified as a primary event. This blood irritates the meninges and surrounding brain tissues, triggering an inflammatory response. In addition, breakdown products of hemoglobin, such as bilirubin, exert toxic effects on brain tissue, exacerbating the damage caused by SAH.

Collectively, these references emphasize the pivotal role of blood within the subarachnoid space in the pathophysiology of SAH. This presence triggers a cascade of events, including inflammation and cerebral vasospasm, which contribute to the clinical manifestations and complications associated with this condition[31].

2.4. Vasospasm and reduced cerebral blood flow

As mentioned earlier, the study conducted by Voldby[30] contributed experimental and clinical data on the pathophysiology of SAH. While not directly addressing vasospasm and reduced blood flow, these data likely enhance a broader understanding of the influence exerted by these factors on the development and progression of SAH.

In a related context, Hayman *et al.*[32] discussed the pathophysiology of acute intracerebral and SAH. They emphasized the impact of reduced blood flow on brain tissue, particularly in the context of SAH. Insufficient blood supply can result in ischemia, contributing to the development of SAH-related complications.

2.5. Seizure burden associated with clinical outcome

A study conducted by De Marchis *et al.*[33] focused on the clinical and functional outcomes in SAH patients with respect to seizures. The study included every patient with spontaneous SAH consecutively admitted and continuously monitored with an electroencephalogram in the neurological intensive care unit at Columbia University Medical Center. The number of hours with seizures recorded on continuous EEG (cEEG) was used to quantify the seizure load. Cognitive results were evaluated using the Telephone Interview for Cognitive Status. In 12% of SAH patients undergoing cEEG monitoring, whose primary purpose was to screen for cerebral ischemia, seizures occurred. Since none of the seizures were convulsive, cEEG would not have detected them. Three months after SAH, a significant correlation was found between the likelihood of a poor functional outcome and the occurrence of both non-convulsive seizures (NCSZ) and seizure load. However, the occurrence of NCSZ alone was not related to cognitive results at 3 months; only the seizure load showed a correlation. The more nuanced relationship between seizure load and cognitive outcome implies that seizure prophylactic measures should not be separated from therapeutic approaches aimed at reducing seizure burden[33].

2.6. Inflammation and immune response

SAH triggers an inflammatory response involving immune cells and the release of pro-inflammatory cytokines, potentially contributing to secondary brain injury[32]. The inflammatory and immune responses in SAH include several key processes:

(i) Blood–brain barrier (BBB) disruption: The presence of blood in the subarachnoid space can lead to the disruption of the blood–brain barrier, allowing immune cells and inflammatory molecules to enter the brain tissue.

(ii) Immune cell activation: Resident immune cells in the brain, such as microglia and macrophages, become activated in response to blood products. They phagocytize red blood cells and release pro-inflammatory cytokines, contributing to neuroinflammation.

(iii) Cytokine release: Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), are released in response to SAH. These cytokines can exacerbate inflammation and neuronal injury.

(iv) Oxidative stress: The breakdown of hemoglobin from the lysed red blood cells leads to the release of heme, generating ROS and causing oxidative stress. This oxidative stress further contributes to tissue damage.

(v) Immune cell infiltration: In some cases, peripheral immune cells may infiltrate the injured brain tissue, amplifying the immune response and potentially contributing to secondary brain injury.

(vi) Perivascular innervation: Cerebral blood vessel contractions are concentration dependent and occur when noradrenaline is administered *in situ* or *in vitro*. It seems that pial veins are more noradrenaline sensitive than pial arterioles. Specifically, α-adrenoceptor blockers can prevent these contractile responses. According to thorough receptor characterizations, the brain vasculature of certain animals (like dogs and cats) has post-junctional α2-adrenoceptors, while adrenoceptors of the α1-subtype are found in the brain vessels of other animals (such as rats, monkeys, and humans)[34].

(vii) Vasoactive neurotransmitters: The cerebral vasculature is densely innervated by sympathetic and parasympathetic nerve fibers, which release various neurotransmitters, including norepinephrine and acetylcholine, regulating vascular tone. In SAH, the balance between these neurotransmitters is disrupted due to the stress response and inflammation, leading to alterations in vascular tone and dysfunction that contribute to SAH. Cardiovascular and cardiac abnormalities are believed to result from sympathetic nervous system activation, which raises circulating catecholamine levels.

(viii) Sympathetic activation: SAH triggers a robust sympathetic nervous system response, resulting in increased norepinephrine release. Norepinephrine induces vasoconstriction of cerebral blood vessels, potentially contributing to DCI in SAH patients. This vasoconstriction can further reduce cerebral blood flow and exacerbate brain injury.

(ix) Inflammatory response: SAH initiates an inflammatory cascade that affects perivascular nerves. Inflammatory molecules, such as cytokines and chemokines, activate or sensitize nerve fibers, thereby enhancing their vasoactive effects. This inflammation-induced neuronal sensitization may result in sustained vasoconstriction, contributing to DCI.

(x) Altered neurotransmitter release: SAH disrupts the release and reuptake of neurotransmitters at perivascular nerve terminals. This dysregulation can lead to sustained vasoconstriction, increased vascular resistance, and impaired autoregulation of cerebral blood flow.

The pathophysiology of complications is illustrated in Figure 2.

2.7. Potential therapeutic targets

Understanding the role of perivascular innervation in SAH pathophysiology provides potential targets for therapeutic interventions. Modulating the activity of perivascular nerves or their neurotransmitters may help mitigate the vasoconstriction and inflammation associated with SAH, thereby improving cerebral perfusion and patient outcomes.

In addition, vascular abnormalities often arise from ruptured intracranial aneurysms or abnormal cerebral blood vessel dilations, leading to the sudden release of blood into the subarachnoid space. Inflammatory responses ensue from the introduction of blood into the subarachnoid space[35].

Hemodynamic disturbances lead to increased intracranial pressure (ICP) and reduced cerebral blood flow due to blood presence in the subarachnoid space, consequently initiating an inflammatory cascade with the

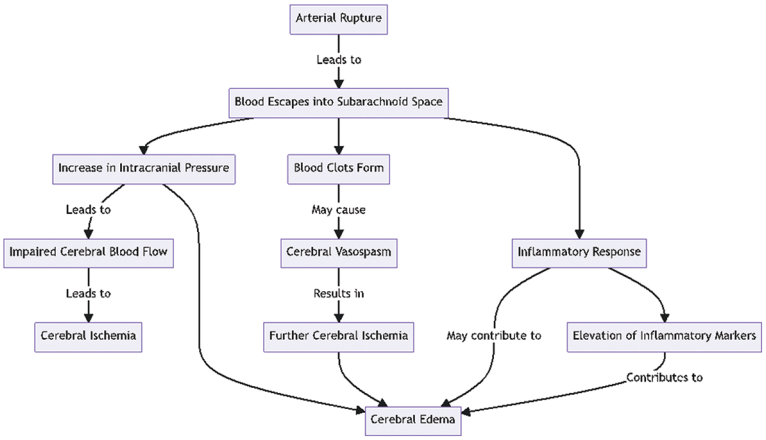


Figure 2. Pathophysiology of subarachnoid hemorrhage complications.

release of inflammatory mediators and contributing to complications such as cerebral vasospasm and DCI[36,37]. SAH leads to cerebral vasospasm, involving the narrowing of cerebral blood vessels due to breakdown products of blood and inflammation, potentially compromising blood flow to brain tissue. SAH primarily stems from ruptured intracranial aneurysms[38], as emphasized in Kellner *et al.*[39]. This rupture leads to an immediate disruption in hemodynamics, causing increased ICP and reduced cerebral blood flow, amplifying the impact of SAH. In addition, inflammatory responses, as highlighted in Cardentey-Pereda and Pérez-Falero[40], are initiated as blood enters the subarachnoid space, contributing to complications such as cerebral vasospasm. This narrowing of cerebral blood vessels can further compromise blood flow to the brain. In summary, the pathophysiology of SAH involves vascular rupture, hemodynamic disruption, and inflammatory processes, collectively contributing to its complex clinical manifestations.

3. Current treatment options

The two basic categories of treatment for SAH are surgical and pharmacologic. Non-contrast computerized tomography (NCCT) is a quick, reliable, and accurate method for identifying SAH[41]. Following an acute episode, a significant proportion of patients with SAH and intracerebral hemorrhage (ICH) showed a two-point decline on the Glasgow Coma Scale[42,43]. The primary goals of care for unstable patients are to secure the airway and continue resuscitative procedures before arriving at the hospital.

3.1. Pharmacologic management

3.1.1. Blood pressure control

During the acute phase, the majority of ICH patients present with high blood pressure when they first arrive. This high blood pressure might lead to hematoma development and a dismal prognosis[43]. The INTERACT2 trial, a major clinical trial that randomly assigned patients to either a blood pressure control group with systolic blood pressure <140 mmHg or a blood pressure control group of systolic blood pressure <180 mmHg for the first 24 h, has provided the most comprehensive data on blood pressure management.

3.1.2. Use of tranexamic acid and factor VII

Tranexamic acid is used to reduce bleeding-related mortality in trauma and postpartum hemorrhage situations. An investigation into the potential of tranexamic acid to reduce hematoma growth and enhance prognosis in adult ICH-related stroke patients was carried out. Adult participants with ICH took part in a randomized controlled trial, and the results demonstrated a significant improvement in patient prognosis, a reduced frequency of hematoma growth, and fewer serious sequelae. These outcomes corroborate the antifibrinolytic properties of tranexamic acid[44].

3.1.3. Antioxidants

One promising medication for the treatment of ICH is edaravone. While it has demonstrated efficacy in patients with ICH, the debate about its long-term advantages and prognosis persists[45]. This potent free radical scavenger[46-50] was initially licensed in Japan[51,52] for the management of acute ischemic stroke (AIS).

3.2. Surgical management

3.2.1. Craniopuncture

Craniopuncture has been the accepted method of treating ICH in China[53]. In a study comparing the results of craniopuncture and conservative management in 377 patients who experienced basal ganglia hemorrhage, researchers discovered that patients undergoing craniopuncture exhibited significantly improved neurological function by the end of 2 weeks, with no variation in the rates of rebleeding and no discernible difference in patient mortality[54].

3.2.2. Craniotomy

While the role of surgery in treating patients with ICH remains a subject of debate, craniotomy for hematoma drainage is the most commonly utilized method in hospitals[55,56]. The surgical study in ICH (STICH)[57] aimed to assess the benefits of prompt hematoma drainage combined with conservative treatment in a multifocal, multinational, randomized clinical study. The study concluded that prompt hematoma drainage did not improve the overall prognosis[57]. However, when significant hematomas impart a mass effect with midline shift causing altered awareness, or when the neurological decline occurs due to hematoma enlargement, a craniotomy becomes an essential life-saving procedure.

3.2.3. Hematoma aspiration and thrombolysis

After a minimum of 5 – 6 h following the computed tomography scan used for diagnosis in stereotactic aspiration with thrombolysis, patients undergo a follow-up scan to assess the stable nature of the clot. In the Minimally Invasive Surgery Plus Alteplase for ICH Evacuation (MISTIE) trials, stereotactic hematoma aspiration with thrombolysis and medical therapy were compared in three stages. The initial published results indicate that the MISTIE approach resulted in a greater reduction in clot volume compared to medical treatment[58].

3.2.4. Neuroendoscopy and evacuation

In the neuroendoscopy and evacuation procedure, the combination of an endoscope and an aspiration cannula is utilized. Research indicates that individuals undergoing endoscopic evacuation had a significantly better prognosis than those receiving medicinal therapy[59].

3.2.5. Surgical clipping and endovascular coiling

Surgical clipping and endovascular coiling are the two most frequently used procedures to lower the incidence rate of bleeding following a superficial arterial hematoma. Surgical clipping involves open surgery performed under general anesthesia. To visualize the aneurysm, the brain is gently retracted, and a tiny clip is positioned across its neck to prevent blood flow into the aneurysm, with titanium clips serving as a permanent fixture on the artery[60]. Despite advancements in endovascular therapy, surgical clipping of paraclinoid aneurysms remains a necessary therapeutic option with a manageable risk profile. The prediction and prevention of post-operative motor impairments during aneurysm clipping have demonstrated feasibility through intraoperative monitoring of motor and somatosensory evoked potentials[61,62].

In endovascular coiling, an initial catheter is used to implant a microcatheter into the femoral artery. The tip of the microcatheter is connected with a platinum coil, and an electrical current is utilized to detach the coil from the catheter once it enters the aneurysm lumen. The coil is left permanently within the aneurysm, inducing thrombosis[60].

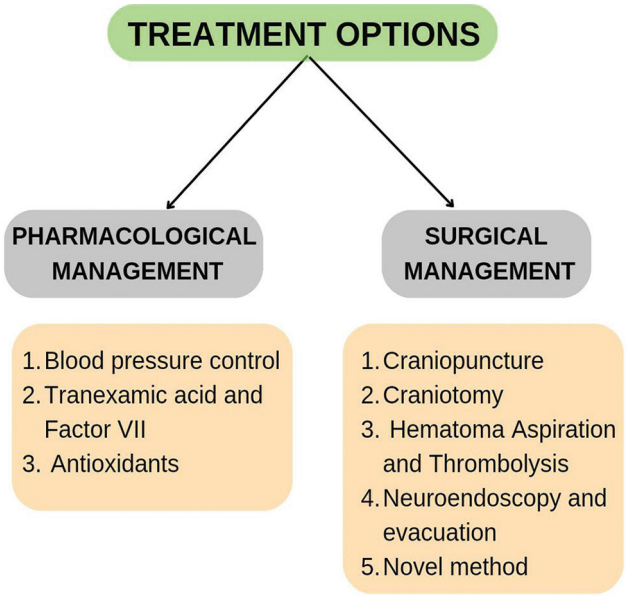


Figure 3. Current treatment options for the management of subarachnoid hemorrhage.

A summary of the current treatment options is illustrated in Figure 3.

3.2.6. Novel surgical method

A study on a case involving a large ICH evacuated utilizing a unique parafascicular BrainPath/Myriad procedure guided by diffusion tensor imaging suggests that this approach is a superior method for rapidly diminishing the hematoma[63].

4. Novel treatment options

SAH is a critical condition associated with a high risk of complications, including vasospasm, cerebral infarction, and poor outcomes. While traditional treatment strategies have limitations, ongoing research is exploring novel approaches to improve the management of SAH. Section 4 outlines several emerging treatment options supported by recent research.

4.1. Exosomes

With their ability to improve cognitive function, inhibit cell death, reduce inflammation, regulate autophagy, and protect the BBB, exosomes show great promise for the treatment of central nervous system (CNS) damage. Certain chemicals and pathways, including microRNA, NF-κB, PI3K/AKT, Notch1, and ERK, collaboratively contribute to these effects. The review by Zhang *et al.* provides an overview of the diverse applications of exosomes in CNS injury, highlighting their importance as therapeutic targets[64].

In comparison to the use of unmodified exosomes, a separate study[65] discovered that administering exosomes derived from human umbilical cord mesenchymal stem cells (hUCMSCs) with miR-206 knockdown confers superior neuroprotective benefits in the context of SAH-induced early brain injury (EBI). By selectively targeting brain-derived neurotrophic factor (BDNF), these miR-206-knockdown exosomes exhibit a considerable capacity to alleviate neurological impairments, reduce brain edema, and mitigate neuronal death. Moreover, *in vivo* administration of exosomes modified with miR-206 activates the BDNF/TrkB/CREB signaling pathway. Essentially, the study[65] confirms that exosomes produced from hUCMSCs with miR-206 knockdown are essential in preventing EBI after SAH by blocking apoptosis through the BDNF/TrkB/CREB signaling cascade. This discovery provides a novel and promising therapeutic target for treating SAH-induced EBI, potentially resulting in better treatment outcomes[66].

Exploring the potential of exosomal miR-3064-5p derived from dendritic cells to restore the BBB in the event of SAH. The results indicate that miR-3064-5p overexpression improves BBB integrity, reduces

inflammation, and mitigates apoptosis in SAH rats by suppressing iNOS expression, enhancing tight junction proteins, and inhibiting the SIRT6/PCSK9 pathway[67]. In SAH rats, the protective effects of dendritic cell exosomes are further reinforced, with miR-3064-5p playing a crucial role in the restoration of BBB following damage. These findings highlight the potential of exosomal miR-3064-5p as a treatment option for SAH, addressing BBB integrity and mitigating damage caused by SAH[67].

4.2. Inhibition of ferroptosis

A study[68] investigating the role of ferroptosis, an iron-dependent regulated cell death process, in SAH revealed that the ferroptosis inhibitor, liproxstatin-1, effectively protected HT22 cells from hemin-induced damage by preserving mitochondrial function and mitigating lipid peroxidation. In *in vivo* experiments, characteristic mitochondrial alterations in cortical neurons following SAH were demonstrated, and liproxstatin-1 treatment attenuated neurological deficits, brain edema, neuronal cell death, and redox imbalance[68]. Ferroptosis inhibition by liproxstatin-1 was linked to the preservation of glutathione peroxidase 4 and the down regulation of acyl-CoA synthetase long-chain family member 4 and cyclooxygenase 2. Furthermore, liproxstatin-1 reduced microglial activation and the release of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α), contributing valuable insights into SAH-related cell death mechanisms for future preclinical investigations[68].

NTN-1 was identified as a potent enhancer of peroxisome proliferator-activated receptor gamma (PPARγ), a key transcription factor governing lipid metabolism. In the context of NTN-1-mediated neuroprotection in SAH, a study investigated ferroptosis, a recently identified form of cell death linked to lipid metabolism[69]. The results demonstrated that NTN-1 treatment significantly improved survival rates, increased neuron survival, and enhanced neurological function, underscoring its role in inhibiting ferroptosis and mitigating neuron death. NTN-1 treatment also upregulated the expression of critical regulators of ferroptosis, including PPARγ, nuclear factor erythroid 2-related factor 2 (Nrf2), and glutathione peroxidase 4 (GPX4), thereby contributing to improved neurological outcomes in SAH. These findings suggest that NTN-1 exerts neuroprotective effects by mitigating neuronal ferroptosis through the PPARγ/Nrf2/GPX4 and coenzyme Q10-ferroptosis suppressor protein 1 (CoQ10-FSP1) pathways, offering valuable insights into potential therapeutic strategies for SAH-induced brain injury[69].

Peroxiredoxin 6 (PRDX6), a recognized antioxidant protein, has been previously linked to ferroptosis and lipid peroxidation, though its role in SAH remains elusive. Moreover, the potential involvement of PRDX6 in the neuroprotective effects of Fer-1, a selective ferroptosis inhibitor, in SAH has not been explored. The study employed endovascular perforation to induce a SAH model and administered Fer-1 and *in vivo* siRNA targeting PRDX6 to investigate the underlying mechanisms[70]. The research confirmed Fer-1's capacity to inhibit ferroptosis and provide neuroprotection in SAH. SAH induction resulted in reduced PRDX6 expression, which Fer-1 ameliorated. Furthermore, Fer-1 effectively addressed dysregulated lipid peroxidation, as indicated by glutathione and malondialdehyde levels, but this effect was reversed by si-PRDX6. Notably, the neuroprotective benefits of Fer-1 in SAH were compromised by PRDX6 knockdown and the use of a calcium-independent phospholipase A2 (iPLA2) inhibitor[70]. These findings underscore the involvement of PRDX6 in SAH-induced ferroptosis and its association with Fer-1's neuroprotective mechanism, particularly through its iPLA2 activity[70].

4.3. Nle^{4}DPhe^7-α-melanocyte-stimulating hormone

A study[71] investigated the potential protective effects of the α-MSH analog Nle^{4}DPhe^7-α- melanocyte-stimulating hormone (NDP-MSH) in experimental SAH in rats. Initial experiments demonstrated that intrathecal injection of low concentrations of NDP-MSH induced a tolerant phenotype in the basilar artery. Systemic treatment with NDP-MSH following SAH significantly reduced vasospasm on day 5. Transcript analysis revealed that SAH caused significant disruptions in the transcriptional profile of the basilar artery, affecting genes related to inflammation, stress response, apoptosis, and vascular remodeling[71]. NDP-MSH treatment mitigated most of these transcriptional changes and reduced the phosphorylation of extracellular-signal-regulated kinases (ERK1/2) and inhibitor protein IκBα. These findings suggest that melanocortins, including NDP-MSH, may serve as safe and effective therapeutic candidates for addressing SAH-related complications, including vasospasm[71].

In a separate study[72], the aim was to investigate the potential of NDP-MSH in reducing oxidative stress and neuronal apoptosis following ICH and to uncover the underlying mechanism. In a mouse ICH model, NDP-MSH was administered intraperitoneally after ICH induction. The results revealed that NDP-MSH treatment effectively mitigated neurological deficits, reduced brain water content, and inhibited oxidative stress and neuronal apoptosis 24 h after ICH[72]. Furthermore, NDP-MSH administration promoted the expression of melanocortin-1 receptor (Mc1r), as well as the phosphorylation of PI3K, Akt, and Nrf2, leading to increased Bcl-2 expression and decreased cleaved caspase-3 levels. Conversely, suppressing

Mc1r expression and PI3K phosphorylation reversed these effects. In conclusion, the study demonstrates that NDP-MSH activation of Mc1r ameliorates oxidative stress and neuronal apoptosis through the PI3K/Akt/Nrf2-signaling pathway in the context of ICH in mice[72].

NDP-MSH, an analog of α-melanocyte-stimulating hormone (α-MSH), was investigated for its anti-inflammatory potential in microglial cells through melanocortin receptor 4 (MC4R). In the pertinent study, NDP-MSH treatment induced the upregulation of the M2a/M2c marker Ag1 and reduced the M2b marker Il-4rα and Tlr4 expression in microglia[73]. Furthermore, it inhibited the nuclear translocation of NF-κB subunits p65 and c-Rel induced by lipopolysaccharide. NDP-MSH effectively reduced TNF-α release triggered by TLR2 and TLR4 agonists, while TLR-induced IL-10 release remained unaffected[73]. Moreover, NDP-MSH inhibited TLR2-induced high mobility group box 1 (HMGB1) translocation and phagocytic activity. These results highlight the potential of melanocortins, particularly NDP-MSH, in attenuating pro-inflammatory mechanisms and promoting M2-like polarization in microglia, offering a promising avenue for immunomodulation in neuroinflammatory disorders[73].

4.4. Glycyrrhizic acid

In a study involving a rat model of SAH[74], the aim was to investigate the therapeutic potential of glycyrrhizic acid (GA) in reducing cerebral vasospasm and to elucidate the underlying mechanisms. Three groups of male rats were established: GA, SAH, and control. The GA and SAH groups received intraperitoneal injections of GA (10 mg/kg) and normal saline (10 mg/kg), respectively, and underwent experimental cerebral vasospasm induction. Following SAH, GA therapy significantly enhanced cerebral function[74]. In comparison to the SAH group, the basilar artery in the GA group exhibited a considerable decrease in vascular wall thickness and a noticeable increase in diameter. Furthermore, in comparison to the SAH group, GA therapy resulted in a significant reduction in *Hmgb1* expression and a decrease in the mRNA expression of *Il-1β*, *Il-6*, and *Tnf-α* but an increase in *Il-10* expression. These results imply that GA may prevent cerebral vasospasm after SAH by inhibiting the expression of HMGB1 and the subsequent generation of inflammatory cytokines[75].

In a mouse model of SAH, a separate study[76] investigated the effects of glycyrrhizin on pro-inflammatory cytokines and peroxisome proliferator-activated receptors (PPARs). The study unveiled morphological alterations in the basilar arteries and decreased PPAR-γ and PPAR-δ protein levels in the SAH groups. Treatment with glycyrrhizin boosted the expression of *Ppar-γ* mRNA and protein, as well as *Ppar-δ* mRNA, which corresponded to lower TNF-α and IL-1β levels[76]. The administration of a PPAR-γ inhibitor prevented the decrease in TNF-α and IL-1β in the groups treated with glycyrrhizin. Glycyrrhizin was linked to the production of PPARs, especially PPAR-γ, and exhibited anti-inflammatory effects on SAH-induced vasospasm overall, indicating its potential use in treating inflammation and vasospasm in SAH[76].

4.5. Proteasomes (HMGB1 and Purpurogallin)

Research into the causes of SAH, specifically immediate and delayed neuroinflammation, has been spurred by the catastrophic consequences of SAH. This process involves a complex role played by T-cell infiltration during SAH. According to a study[77] examining this process, purpurogallin demonstrates potential in mitigating early inflammation and subsequent stimulation of HMGB1 in a mouse model of SAH. This suggests that the natural polyphenol purpurogallin may hold therapeutic promise for treating and preventing SAH-induced vasospasm. Nevertheless, the work is constrained by its inherent limitations, warranting the necessity for future research to consider variables such as SAH-induced vascular remodeling and the current paucity of comprehensive mechanistic evidence[77].

Rhinacanthin-C (RCT-C) demonstrates neuroprotective properties by decreasing cleaved caspase-3 and caspase-9a, mitigating apoptosis. Its anti-inflammatory effect is evident in the RCT-C groups, as indicated by the decreased expression of HMGB-1 mRNA and protein. Importantly, the administration of HMGB-1 recombinant protein counteracts the neuroprotective and immunosuppressive effects of RCT-C. This finding suggests that RCT-C influences the HMGB-1 pathway and mitigates brain apoptosis in the context of SAH pathogenesis[78].

In the basilar artery of SAH rat models, HMGB1 is released from smooth muscle cells through a dynamic process[78]. Anti-HMGB1 monoclonal antibodies (mAb) efficiently blocked this cascade of events, which included the migration of HMGB1, upregulation of receptors constricting blood vessels, and the presence of inflammation-linked chemicals. The use of anti-HMGB1 mAb contributed to the relaxation of blood vessel constriction in the context of SAH. This treatment approach successfully interrupted the sequence by neutralizing extracellular HMGB1, preventing inflammatory responses, alleviating severe blood vessel constriction in the basilar artery, and ultimately decreasing brain damage caused by insufficient blood flow, thereby improving neurological symptoms. These results suggest that anti-HMGB1 mAb therapy can effectively disrupt the series of events triggered by SAH[78].

Table 1. All available treatment options for subarachnoid hemorrhage

Treatment types	Pharmacologic treatment	Surgical treatment	Novel therapies
Treatments	Blood pressure control	Craniopuncture	Exosomes
	Tranexamic acid	Craniotomy	NDP-MSH
	Factor VIII	Hematoma aspiration and thrombolysis	Proteosomes-HMGB1, and purpurogallin
	Antioxidants	Neuroendoscopy and evacuation	Liproxstatin-1
			Glycyrrhizic acid
			Clazosentan and endothelin receptor antagonists

Abbreviations: HMGB1: high mobility group box 1; NDP-MSH: Nle4DPhe7-α-melanocyte-stimulating hormone.

4.6. Clazosentan and endothelin receptor antagonists

Clazosentan, an endothelin receptor antagonist, has demonstrated promise in preventing cerebral vasospasm and improving outcomes post-SAH. Clinical trials, such as CONSCIOUS-1 and CONSCIOUS-2, have substantiated their efficacy in reducing the incidence of vasospasm-related morbidity[79,80].

4.7. Calcium antagonists for SAH

A Cochrane systematic review explored the use of calcium antagonists in the management of aneurysmal SAH, with the aim of determining their effectiveness and safety[81]. The insights derived from these clinical trials and systematic reviews have contributed significantly to advancing our knowledge of treatment strategies for SAH, which helps to improve patient outcomes and reduce complications associated with this condition.

4.8. Triple-H therapy optimization

Triple-H therapy has long been used to prevent vasospasm. Recent research, however, emphasizes the importance of individualizing its components to achieve optimal cerebral perfusion while mitigating potential complications[82]. Triple-H therapy involves the manipulation of hemodynamic parameters, namely hypertension, hypervolemia, and hemodilution. The principles, controversies, and outcomes associated with triple-H therapy can be explored in scholarly articles[80,81,83-86], which cover topics including:

(i) The rationale behind inducing hypertension to improve cerebral perfusion.
(ii) The role of hypervolemia in preventing DCI.
(iii) The use of hemodilution to reduce blood viscosity and enhance microcirculation.
(iv) Challenges in achieving the delicate balance of these parameters.

4.9. Intracranial pressure monitoring

Intracranial pressure monitoring plays a crucial role in identifying and managing secondary insults post-SAH.

Table 2. Clinical trials on subarachnoid hemorrhage (SAH)

Clinical trials	Details of the clinical trials
CONSCIOUS-1 Trial	The CONSCIOUS-1 trial aimed to investigate the potential of clazosentan, an endothelin receptor antagonist, in preventing neurological ischemia and infarction following SAH[91]. This randomized, double-blind, placebo-controlled phase 2 trial assessed the drug's effectiveness and safety in improving outcomes for SAH patients.
CONSCIOUS-2 Trial	Building upon the findings of CONSCIOUS-1, the CONSCIOUS-2 trial expanded the investigation into clazosentan's efficacy in SAH patients undergoing surgical clipping[79]. This phase 3 trial continued to explore its potential in preventing adverse neurological outcomes post-SAH.
STASH Trial	The STASH trial investigated the use of simvastatin, a statin medication, in patients with aneurysmal SAH[80]. This multicenter, randomized phase 3 trial aimed to determine whether simvastatin could improve patient outcomes and reduce complications following SAH.

Recent systematic reviews highlight its importance in guiding treatment decisions and improving patient outcomes[87]. ICP monitoring is critical in SAH management, allowing continuous assessment of intracranial dynamics. Numerous scholarly articles explore relevant topics[81,82,88,89], covering topics including:

(i) The importance of ICP monitoring in identifying and managing elevated ICP.
(ii) Various monitoring techniques, including intraventricular and intraparenchymal monitors.
(iii) The correlation between elevated ICP and poor outcomes in SAH patients.
(iv) Controversies surrounding the threshold for intervention based on ICP values.

4.10. Statin therapy

Statins, particularly simvastatin, have exhibited potential in reducing the incidence of vasospasm and improving clinical outcomes post-SAH. The STASH trial demonstrated the safety and efficacy of statins in this context[81]. Table 1 provides a summary of all available treatment options.

4.11. Modified Fisher scale for risk prediction

Recent studies have emphasized the utility of the modified Fisher scale in predicting symptomatic vasospasm and cerebral infarction post-SAH. This scale enables risk stratification, allowing for more targeted interventions in high-risk patients[90]. The development of outcome prediction models, exemplified by the SAHIT multinational cohort study, aids in identifying patients at a higher risk of complications, allowing for targeted interventions and improved outcomes[91].

4.12. Clinical trials

Table 2 mentions the major clinical trials.

5. Conclusion

SAH is a severe and often fatal condition across all age groups, stemming from different causes. The treatment landscape for SAH is a subject of ongoing discussion, with a recognition of the need for tailored treatment options to address the specificity of each patient. SAH carries a high risk of complications, including vasospasm, cerebral infarction, and poor prognosis.

Traditional treatment strategies exhibit limitations, prompting the exploration of novel approaches to improve the management of SAH. The two basic categories of SAH treatment are surgical and pharmacologic. NCCT has emerged as a rapid, reliable, and accurate diagnostic method for SAH. Pharmacologic treatments mainly involve blood pressure control, the use of tranexamic acid, factor VIII, and antioxidants. Surgical treatments encompass craniopuncture, craniotomy, hematoma aspiration and thrombolysis, neuroendoscopy, and evacuation. Novel therapies, such as exosomes, demonstrate the ability to improve cognitive function, inhibit cell death, reduce inflammation, regulate autophagy, and protect BBB. The utilization of exosomes holds great promise for treating damage to CNS.

The ferroptosis inhibitor, liproxstatin-1, has proven effective in protecting HT22 cells from hemin-induced damage by preserving mitochondrial function and mitigating lipid peroxidation. These findings suggest that NTN-1 exerts neuroprotective effects. Systemic treatment with NDP-MSH following SAH significantly reduces vasospasm. Glycyrrhizin has been linked to the production of PPARs, especially PPAR-γ, and exhibits anti-inflammatory effects on SAH-induced vasospasm, suggesting its potential for treating inflammation and vasospasm in SAH. The use of anti-HMGB1 mAb contributes to the relaxation of blood vessel constriction in the context of SAH. This treatment method effectively interrupts the sequence by neutralizing extracellular HMGB1, preventing inflammatory responses, alleviating severe blood vessel constriction in the basilar artery, and ultimately decreasing brain damage caused by insufficient blood flow, thereby improving neurological symptoms. Clazosentan, an endothelin receptor antagonist, has demonstrated promise in preventing cerebral vasospasm and improving outcomes post-SAH.

The above-mentioned treatment options are some of the novel therapies available for the treatment of SAH. Predictably, numerous future therapies may target the pathophysiology mechanisms mentioned in this review. The treatment of SAH can be approached in an individualistic manner, involving the use of combinations of newer therapies with previously available surgical or medical options based on patient requirements. Tailoring treatment to each patient's specific needs could potentially reduce the incidence of complications and provide exclusively specific treatments. This approach provides a foundation for future research to explore these novel therapies and manage different types of patients with unique combinations indicated for specific patients. Ultimately, this may contribute to the development of updated guidelines for future reference.

The major limitation of this review lies in the challenge of evaluating the combinations of novel therapies mentioned alongside the traditional therapies currently available.

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The authors declare that they have no competing interests.

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