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Research Article

Vasospasm Management Strategies

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ABSTRACT

Aim- In this study, we present a broad presentation of the current state of cerebral vasospasm, including its pathogenesis, commonly used treatments, and future outlook.
Methods- A literature review was conducted for cerebral vasospasms using the PubMed journal database (https://pubmed.ncbi.nlm.nih.gov). Relevant journal articles were narrowed down and selected using the Medical Subject Headings (MeSH) option in PubMed.
Results- Cerebral vasospasm is the persistent narrowing of cerebral arteries days after experiencing a subarachnoid hemorrhage (SAH). Eventually, if not corrected, this can lead to cerebral ischemia with significant neurological deficits and/or death. Therefore, it is clinically beneficial to diminish or prevent the occurrence or reoccurrence of vasospasm in patients following a SAH to prevent unwanted comorbidities or fatalities. We discuss the pathogenesis and mechanism of development that have been implicated in the progression of vasospasms as well as the manner in which clinical outcomes are quantitively measured. Further, we mention and highlight commonly used treatments to inhibit and reverse the course of vasoconstriction within the cerebral arteries. Additionally, we mention innovations and techniques that are being used to treat vasospasms and the outlook of their therapeutic value.
Conclusion- Overall, we give a comprehensive summary of the disease that encapsulates cerebral vasospasm and the current and future standards of care that are used to treat it.

Key Words: *subarachnoid hemorrhage; vasospasm; treatment; transcranial doppler.*

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INTRODUCTION

Cerebral vasospasm is defined as arterial narrowing and vasoconstriction following a hemorrhage in the subarachnoid space, most commonly classified as a SAH**(Fig. 1)**. In a study of more than 30,000 patient cases, it was found that the incidence of angiographic vasospasm after SAH was 43.3% and another 32.5% demonstrated symptoms of delayed ischemic deficit (DIC)[1].

Vasospasm begins 3 days following a SAH, peaks at 7 days, and declines in incidence after 21 days[2].Another study found thatof the patientswho demonstrated angiographic vasospasm, 90.4% of them revealed symptoms by day seven [3].In order to screen and monitor for vasospasms, the method varies widely by region [4].Commonmethods include transcranial Doppler (TCD) ultrasonography, computed tomography angiography (CTA), computed tomography perfusion (CTP)magnetic resonance angiography (MRA), magnetic resonance perfusion (MRP), and digital subtraction angiography (DSA) [4-6].

The primary goal of acute vasospasm treatment is local arterial vasodilation to prevent delayed cerebral ischemia (DCI) [7]. This progression to ischemia depends on a multitude of factors including the severity of vasospasm as well as its rapid diagnosis and treatment upon presentation. DCI is an advanced stage of angiographic vasospasm where significant narrowing of blood vessels has led to ischemia.It is the major cause of death and disability in patients who had a SAH [4].Symptomatic vasospasm is defined as a reduced level of consciousness and/or neurological deficit occurring after a SAH with confirmed angiographic vasospasm [8,9]. Not all patients who develop angiographic vasospasm will develop symptomatic vasospasm [9].

One study conducted on 2,741 patients who suffered from SAH demonstrated that SV occurred in 30% of the patients, and of this number, 45% presented with cerebral infarction.Of the patients who did not express SV, 18% still experienced a cerebral infarction [10].While vasospasm is considered one of the several risk factors that eventually lead to cerebral ischemia[1], cigarette smoking, hypertension[11],and serum glucose/potassium ratio [12]are all involved and may be important to assess.

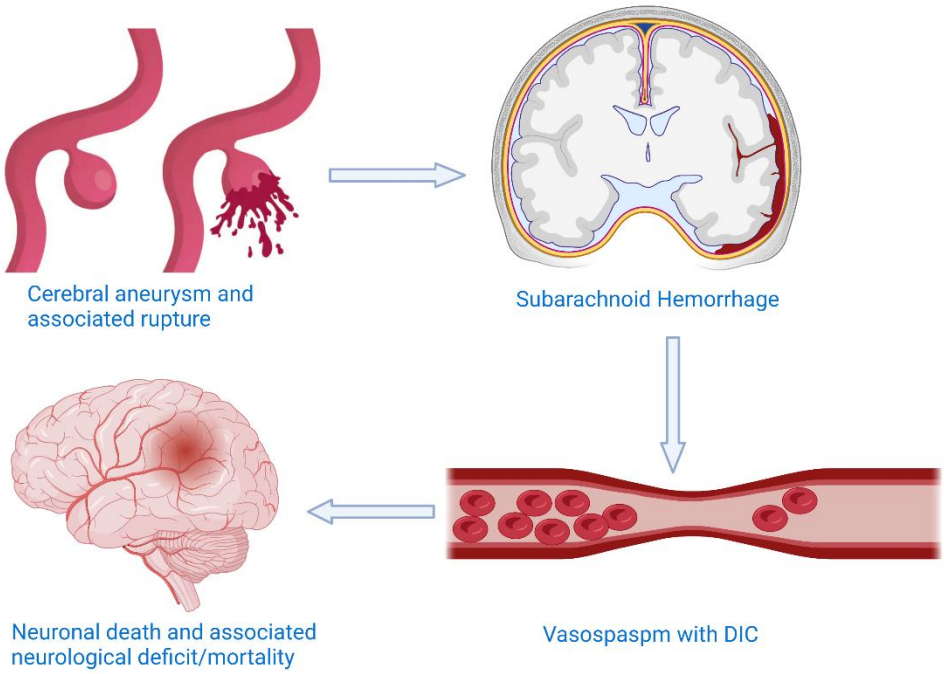

Fig.1. Flow map for the development of vasospasm and its potential destructive effect.

Material and Methods

A literature review was conducted for cerebral vasospasms using the PubMed journal database (https://pubmed.ncbi.nlm.nih.gov). Relevant journal articles were narrowed down and selected using the Medical Subject Headings (MeSH) option in PubMed.

Result

Pathogenesis

Following a SAH, cerebral ischemia and other pathological abnormalities are referred to as early brain injury[2].During this phase, there is an increase in the activity of NADPH oxidase which leads to the increased production of reactive oxygen species (ROS)including hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), hydroxyl radical (OH^-), and peroxynitrite (ONOO) [13,14].The ROS that isgenerated inducesdetrimental and irreversible lipid peroxidation as well as DNA and protein breakdown [15,16]. Oxyhemoglobin, a product of erythrocyte lysis, is released into the subarachnoid space due to aneurysm rupture and induces endothelin-1 (ET-1). ET-1 subsequently leads to intracellular Ca^{2+} influx and vasoconstriction [2,17].

The major driving factor for vasoconstriction is the increase in intracellular Ca^{2+} levels throughinflux from extracellular Ca^{2+} and simultaneous Ca^{2+} release from the sarcoplasmic reticulum [18]. This is regulated by the phosphorylation of MLC by Ca2+/calmodulin-regulated myosin light chain kinase (MLCK) and the inhibition of myosin phosphataseby Rho, a Ras family G protein. Rho, a GTPase, activates Rho-kinase and phosphorylates myosin phosphatase at the myosin binding subunit, therebyinactivating it [19-21].The increased intracellular Ca^{2+} levels drive its binding to calmodulin which producesa conformational change allowing calmodulin to bind to MLCK. Once bound tocalmodulin, MLCK is activated and can phosphorylate MLC. This action allows actin and myosin to progress through theircross-bridge cycle and produce force generation that leads to smooth muscle vasoconstriction [22,23].

Two important factors that lead to cerebral vasospasms following SAH are NO and ET-1. NO is a free radical gas that is produced from nitric oxide synthase (NOS).[24] NO induces downstream effects that lead to the inhibition of intracellular calcium release by inhibiting phospholipase C and inositol-1,4,5-trisphosphate [25,26]. Therefore, NO has an antagonistic effect on smooth muscle vasoconstriction. Another molecule, hemin, derived from methemoglobin that is present in the subarachnoid space following a SAH, induces iNOS, which generates NO. This might seem counterintuitive as NO would attenuate the severity of vasospasm. However, hemin leads to excessive levels of NO which produce toxic effects when they generate free radicals such as OH^- and $ONOO^-$and cause lipid peroxidation. These ROS contribute to the development of vascular injury associated with cerebral vasospasm after SAH [27,28]. They promote lipid peroxidation that weakens the plasma membrane and increases the membrane permeability to ions [29].

This damage is thought to play a role in the development of vasospasm through several mechanisms:(1) constitutive nitric oxide synthases (NOS) areinhibited, (2) there are increased cerebrospinal fluid (CSF) levels of asymmetric dimethyl-L-arginine (ADMA), the endogenous inhibitor of NO synthase, and (3) oxyhemoglobin scavenges and reduces the levels of NO [30]. The constitutive NOS are composed of type I and type III, which release NO from neurons and blood vessels, respectively.Several studies report decreased levels of type I and type III NOS during the peak of vasospasm and link their decreasedlevels with a potential originating factor [31-35]. Additionally, ADMA has been shown to increase in the CSF of primates and humans during the time course of vasospasm and also decrease with vasospasm resolution [36-37]. Furthermore, the release of oxyhemoglobin following an aneurysm rupture scavenges NO and eliminates it from the blood vessels [38].

ET-1 is a 21 amino acid peptide that is generated from post-translational modifications of a larger ~212 amino acid peptide precursor by endothelin-converting enzyme [39-41]. ET-1 is produced by a variety of different cell types including endothelial cells [42,42], macrophages [44], and astrocytes [45-47].It is a powerful long-lasting vasoconstrictor that is generated in endothelial cells after ischemia or shear stress**(Fig. 2)**. ET-1 binds to smooth muscle cells and leads to the formation of inositol triphosphate [48]. Under physiological conditions, ET-1 cannot penetrate the blood-brain barrier[49,50]and therefore, either requires a damaged endothelium or must act on the tunica adventitia to exert its vasoconstrictive effects [51,52].

ET-1 is implicated in vasospasms as one study found the concentration of ET-1 to be significantly higher in patients with vasospasm compared to patients without symptomatic vasospasm [53]. Vasospasm of the cerebral arteries usually occurs after a stroke and the longer it lasts, the more brain damage there is. Therefore, inhibition of ET-1 or antagonists of its vasoconstrictive effects are potential therapeutic targets. As a result, it has been shown using animal models, that smooth muscle endothelial receptor A (ET_A) antagonists improve the outcomes of ischemic brain injury [39,54].

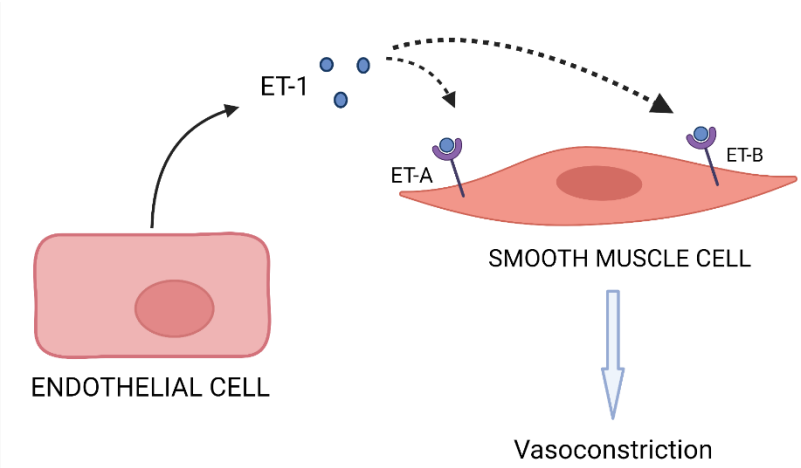

Fig.2. ET-1 effect on smooth muscle cells

Current Management Strategies for Vasospasms

Nimodipine

Nimodipine is second-generation voltage-gated L-type calcium channel antagonist that was initially indicated for use treating systemic hypertension due to its vasodilatory properties. Due to its lipophilic nature, it can permeate through the blood-brain barrier and act on cerebral vasculature [55]. Thus, nimodipine has been indicated for counteracting constriction due to vasospasms secondary to SAHs and decrease morbidities related to vasospasms [56-59].Additionally, nimodipine is reported to have neuroprotective properties that assist in good patient outcomes, outside of its vasculature effects [60-62]. In fact, previous studies have determined that nimodipine, through its inhibition of L-type calcium channels, protects against oxygen-glucose deprivation commonly induced by ischemia, which can possibly result from vasospasms [57,63]. Typically, nimodipine is administered to patients orally as a first-line preventative measure against vasospasms in patients with SAHs and viaarterial injections for medically refractory vasospasms [56,60].

Balloon Angioplasty

Despite its effectiveness, some patients fail to respond to Nimodipine when managing vasospasms. For these patients, endovascular procedures, such as balloon angioplasty and arterial injections, are indicated to be a more viable option [64].Balloon angioplasty, otherwise known as percutaneous transluminal angioplasty, entails entering a catheter with an inflatable balloon tip into vasculature and expanding that balloon to reestablish normal blood flow [65].The exact mechanism of action underlying balloon angioplasty remains unknown, but previous studies have demonstrated possible structural changes due to balloon angioplasty that may contribute to the cessation of vasospasms [66]. Scanning electron

microscopy following dilatation with balloon angioplasty has shown the presence of stretched-outand sometimes torn collagen fibers in the tunica adventitia, leading researchers to postulate that these changes help increase arterial compliance and decrease the likelihood of vasospasms [67].

As an endovascular procedure, the effectiveness and difficulty of a balloon angioplasty procedure is contingent on the nature of the vasculature targeted. For example, it is noted that a balloon angioplasty of the middle cerebral artery (MCA)is relatively simple and generally met with favorable outcomes, and as such is preferred for treating vasospasms localized to the MCA [65,68]. However, the same balloon angioplasty procedure is considered high-risk for the anterior cerebral artery (ACA) due to its sharper angles of navigation and smaller luminal diameter, thus relegating the procedure to other lower-risk alternatives [65].In fact, one comparative study noted that there was only a 34% success rate with balloon angioplasties targeting the ACA, compared to a 94% success rate in the proximal MCA [66,69].In 70% of these unsuccessful attempts, the balloon was prevented from advancing due to challenging angles or the severity of the presented vasospasms [69].Indeed, this touches upon a major limitation of balloon angioplasty that has allowed the establishment of other endovascular procedures, including arterial injections, to manage vasospasms, as balloon angioplasty is contraindicated from application in distal aspects of cerebral vasculaturedue totechnical challenges resulting from thinner arterial walls and complex vascular navigation [66,70]. Additionally, balloon angioplasty procedures can possibly result in arterial dissection, vessel rupturing, thromboembolism, and branch occlusion, all often lethal complications that require consideration beforeconducting balloon angioplasty [64,71,72].

Arterial Injections

The complications and challenges in navigation associated with balloon angioplasties pushed the development and utilization of arterial injections as an alternative to treat vasospasms [64].This endovascular procedure typically deliversvasodilatory drugsvia microcatheterization, at times with the assistance of anticoagulants such as hirudin and antiplatelets, including aspirin and ticlopidine [73,74].The primary agent associated with arterial injections treating vasospasms is papaverine, although other drugs such as nimodipine, nicardipine, and mannitol have been used before as well [64,73,75].Arterial injections of a vasodilatory agent is commonly combined with hypertensive hypervolemic hemodilution therapy, otherwise known as “Triple-H” therapy [73,76].

Despite its effectiveness in treating mild to moderate cases of vasospasms, arterial injections of papaverine have been met with complications due to the pharmacologic nature of the drug. For example, it has been described that papaverine has a relatively short half-life, and as such, results in a decreased duration of action and limits its use in more severe cases of vasospasms [64]. Furthermore, previous studies have also shown a reversal in action, including narrowing of vasculature, following the application of papaverine, which could possibly be due to decreased tissue sensitivity or histological changes [64,77-79].

Stent Retrievers

One emerging and considerable standard method of care that has been introduced to treat vasospasm has been the use of self-expandable retrievable stents. The use of stent retrievers for mechanical thrombectomy has become a standard therapy and has been widely adopted over the past couple of years [80]. A stent retriever device works by applying a variable centrifugal force against the vessel endothelium using a hollow mesh tube**(Fig. 3)**. The force of the mesh tube is inversely proportional to the diameter of the vessel.Therefore, as the lumen diameter decreases, a greater radial force is generated and as the diameter increases, less radial force is generated [81]. This method has typically been used to perform a mechanical thrombectomy to achieve long-lasting vasodilation [82]. Compared to intraarterial (IA) vasodilators such as verapamil, nimodipine, and nicardipine, stent retrievers have been shown to be longer-lasting in their effects [83]. When treated solely with stent retrievers, patients commonly require no further intervention compared to when they are only injected with IA vasodilators. Frequently, IA vasodilators require multiple rounds of treatment within a small period of time [84]. However, there is no limit to the simultaneous use of stent retrievers and vasodilators. Patients can be administered vasodilators immediately after the application of a stent retriever to maximize vasodilatory action [85]. Additionally, as the flow rate of a vessel is inversely proportional to the length of the vessel, the more distal the location of the occluded vessel, the less flow is supplied. Balloon angioplasty fails in this regard to vasodilate distal vessels and instead it is confined to larger and more proximal vessels such as the proximal internal cerebral artery or MCA, whereas stent retrievers can reach distal segments of the internal cerebral artery, such as A2 and M2 [86]. Thus, stent retrievers have a broader range of applications compared to balloon angioplasty as they are not limited in their area of activity. Another benefit of using stent retrieversis their ability to provide a constant blood supply during the intervention. During the procedure, the stent does not occlude blood flow through the vessel as it is composed of a hollow interior. On the other hand, balloon angioplasty temporarily occludes blood flow which amplifies the already limited perfusion due to cerebral vasospasm [87]. These side effects of decreased blood flow and brain tissue perfusion reduce the favorability of patient outcomes compared to stent retrievers.

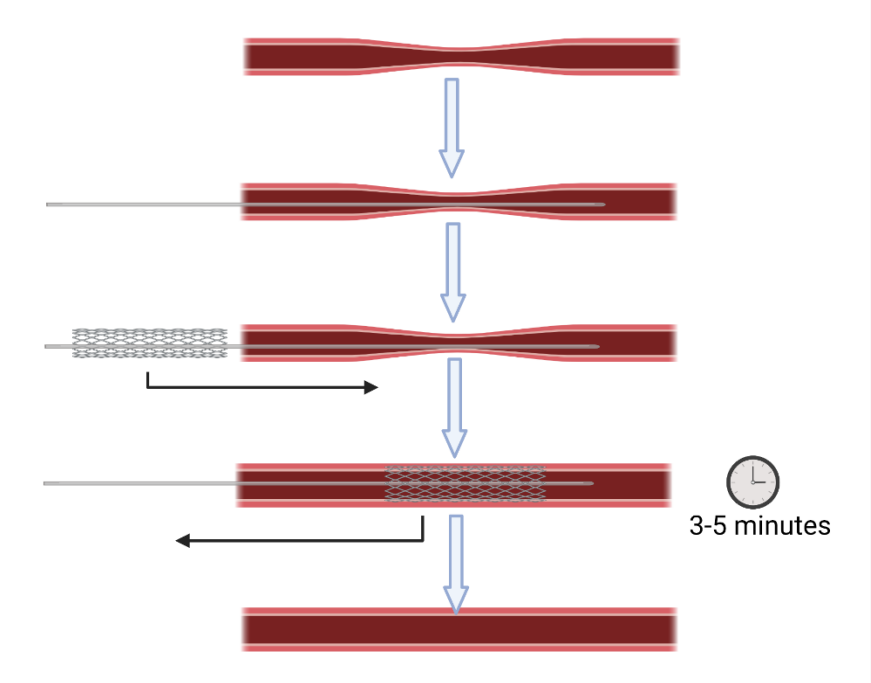

Fig.3. Stent retrievers used for vasoconstriction of vasospastic vessels

New Investigations and Mechanistic Targets.

As aforementioned, TCD and DSA are currently the primary techniques used to screen for vasospasms, with DSA being the gold standard for both medium and large vasospasms. Recently, novel models of TCD are being tested to detect cerebral autoregulation, allowing for the measurement of resting blood flow in the cerebral arteries [88]. Many other new investigations and advancements in the treatment of vasospasms have been in the realm of arterial injection medications. Currently, the only agent with Class 1 evidence for reduction of adverse outcomes in patients has been nimodipine [89,90]. However, many advancements and novel therapeutics are currently being evaluated and show potential effectiveness in protecting against DCI, but further research needs to be done. Additional various small studies have shown potential in efficacy for the intervention of SAH-induced pathologies through intra-arterial vasodilators such as fasudil, intrathecal, and nicardipine[90]. Intra-arterial infusion of fasudil hydrochloride has recently been used for the treatment of cerebral vasospasm secondary to bacterial meningitis and has been shown to be effective [91]. Fasudil has been seen to be just as if not more effective than nimodipine for cerebral vasospasm prevention and is associated with relatively few side effects.[91]

Other novel investigations have also focused on mitigating balloon angioplasty-related limitations, as we have previously mentioned. Recently, the FDA approved Comaneci angioplasty for the treatment of symptomatic refractory vasospasm [92]. Traditionally, the Comaneci device is used to bridge patients to an event remodeling embolization technique. However, studies have shown sufficient vasospasm improvement over various time periods [92,93]. Moreover, Comaneci is relatively flexible in maneuvers in contrast to balloon angioplasty, which is limited in its targets to proximal large vessels [65]. Similarly, the Solitaire stent receiver device has been seen to have potential in treating vasospasms, as it avoids the risks that balloon angioplasty carries such as vessel rupture and limitation in targeting vessels of smaller size [86,94]. Additionally, Solitaire's adaptability to the size of the vessel and force delivered along with the ability to target smaller vessels has made it recently attractive as a therapeutic. Recent studies have shown its effectiveness in more distal intracranial vessels (A2 and M2 branches) as well [86]. The ability to reach distal portions of the internal cerebral artery rather than be limited to the proximal cerebral artery or MCA shows the potential of Solitaire compared to prior techniques. Further research must be done in this field to find more consistent and reliable therapeutics to increase the prevention and earlier intervention of SAH-induced vasospasms.

Measurement of Clinical Outcomes.

Acute cerebral vasospasms must be managed urgently to reduce the duration of any associated cerebral ischemia, which may progress to infarction and pose life-threatening consequences [7]. Pre-intervention assessment of the location and extent of associated cerebral ischemia or infarction can be achieved via several imaging modalities, including TCD, CTA, CTP, MRA, MRP, and DSA as mentioned above [4-6].Similarly, these same imaging modalities may be used to objectively assess for successful re-perfusion to ischemic or infarcted tissue immediately following intervention [95].Clinical outcomes following re-perfusion may also be evaluated by monitoring several biochemical indicators which are directly associated with cerebral ischemia to provide a more immediate objective assessment of clinical progress.Several such indicators include stress-induced increases in NOS and NADPH oxidase activity, which generate

elevated levels of ROS byproducts that are associated with systemic toxicity [2].Although some pathological changes caused by ROS toxicity may be irreversible, successful re-perfusion following vasospasm-induced cerebral ischemia can be biochemically indicated by declines in NOS activity, NADPH oxidase activity, and ROS levels. Monitoring the levels of NO and ET-1 may also serve as additional biochemical markers, where an increase in NO levels and decrease in ET-1 levels are associated with vasodilation and may be indicative of vasospasm cessation [28]. Functionally, clinical outcomes following intervention may be assessed by comparing a patient's pre-intervention and post-intervention Glasgow Coma Scale (GCS) score and motor strength, as studies have reported considerable increases in both measures within 24 hours of intervention**(Fig. 4)**[96,97].Although successful re-perfusion may be functionally indicated by increases in both GCS score and motor strength, it is important to mention that several factors – such as the severity, extent, location, and duration of vasospasm-induced cerebral ischemia – may have significant impacts on a patient's ability to return to baseline levels of functionality, with respect to GCS score, motor strength and cognition [96,98]. While low GCS scores might be indicative of the development of vasospasm in a patient [99], others have used modified scoring methods that combine other scales, such as the modified Fisher scale,to more accurately predict vasospasms [100].

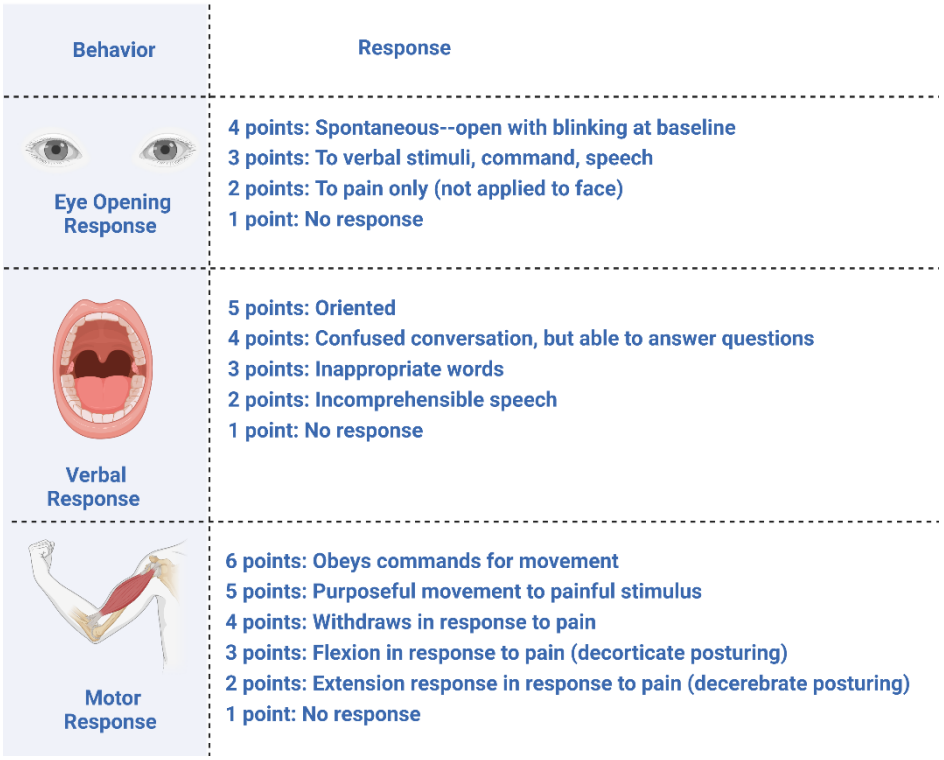

Fig.4. GCS to determine the level of consciousness in a patient [101].

CONCLUSION

In this review, we described the mechanism of vasospasm development, commonly used treatment methods, the method of measuring clinical outcomes, and novel investigations for its mechanistic targets. We explained the occurrence of vasospasm following SAH and the threat it poses as a potential cause for cerebral ischemia and neurological deficits. We examined the central role of NO and ET-1 in the pathophysiology of vasospasm development and discussed the antagonist effects they exert on the cerebral endothelium. Furthermore, we mentioned the use of several common endovascular treatment therapiesas well as vasodilators currently used in clinical protocols and compared their strengths and weaknessto each other. While vasospasm might be common and anticipated following a SAH, it is difficult to measure without evidence of a neurological deficit. Finally, we commented on the use of GCS to measure and monitor the status of a patients return to baseline functionality.

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