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Review Article

Management of aneurysmal subarachnoid hemorrhage: State of the art and future perspectives

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Abstract

Background: Aneurysmal subarachnoid hemorrhage (SAH) accounts for 5% of strokes and carries a poor prognosis. It affects around 6 cases per 100,000 patient years occurring at a relatively young age.

Methods: Common risk factors are the same as for stroke, and only in a minority of the cases, genetic factors can be found. The overall mortality ranges from 32% to 67%, with 10–20% of patients with long-term dependence due to brain damage. An explosive headache is the most common reported symptom, although a wide spectrum of clinical disturbances can be the presenting symptoms. Brain computed tomography (CT) allow the diagnosis of SAH. The subsequent CT angiography (CTA) or digital subtraction angiography (DSA) can detect vascular malformations such as aneurysms. Non-aneurysmal SAH is observed in 10% of the cases. In patients surviving the initial aneurysmal bleeding, re-hemorrhage and acute hydrocephalus can affect the prognosis.

Results: Although occlusion of an aneurysm by surgical clipping or endovascular procedure effectively prevents rebleeding, cerebral vasospasm and the resulting cerebral ischemia occurring after SAH are still responsible for the considerable morbidity and mortality related to such a pathology. A significant amount of experimental and clinical research has been conducted to find ways in preventing these complications without sound results.

Conclusions: Even though no single pharmacological agent or treatment protocol has been identified, the main therapeutic interventions remain ineffective and limited to the manipulation of systemic blood pressure, alteration of blood volume or viscosity, and control of arterial dioxide tension.

Key Words: Outcome, subarachnoid hemorrhage, treatment, vasospasm

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INTRODUCTION

Subarachnoid hemorrhage (SAH) following a ruptured intracranial aneurysm accounts for approximately 5% of the strokes.[6] It affects a relatively young age, and it is associated with a poor prognosis.[6]

The incidence of SAH is 10.5 per 100,000 person years (approximately 27000 patients per year)[57] and the average age of patients with SAH is significantly lower than for other types of stroke, peaking in the sixth decade.[53] Gender and region have a marked influence on the incidence of SAH. Women have a 1.6 times higher risk than men,[57] and black people have a 2.1 times (95% CI: 1.3–3.6) higher risk than whites.[11] In Finland and Japan, the incidence is reported to be greater than in other parts of the world. Autopsy studies show that cerebral aneurysms are rather common in adults with a prevalence ranging between 1% and 5%.[108] Therefore, 1 million to 12 million Americans harbor intracranial aneurysms.

Outcome after aneurysmal SAH depends on several factors, including the severity of the initial hemorrhage, rebleeding, perioperative medical management, and the timing and technical success for aneurysm exclusion from the cerebral circulation.

The overall mortality rates from 32% to 67% with 10–20% of patients with long-term dependence due to brain damage.[34] In this regard, 12% of the patients die before medical treatment can be given and 25% die within the first 24 hours.[12] A further 40–60% mortality occurs within 30 days.[12] Among the surviving patients, approximately one-third remain dependent.[34] In a study focusing on the quality of life in patients after SAH, only 9 of 48 (19%) who were independent 4 months after the hemorrhage had no significant reduction in quality of life.[36] After 18 months, only 15 of the 48 patients (31%) had no reduction in the quality of life.[36] Accordingly, only a small minority of all patients with SAH had a good outcome.

Despite advances in diagnostic, neurosurgical, and anesthetic techniques as well as preoperative and postoperative management of patients, the ultimate overall outcome in patients with aneurysmal SAH remains unsatisfactory. Many issues are still without a solution regarding the clinical management of SAH, although research has been accumulated in the past decade. Ongoing and future studies blossomed from what we have learned and hold promise for the development of effective strategies to improve SAH outcome.

ETIOLOGY AND RISK FACTORS

Epidemiologic studies show that 7–20% of patients with aneurysmal SAH have a first or second-degree relative with a confirmed intracranial aneurysm.[73] Accordingly, the familial predisposition to SAH is an important and non-modifiable risk factor.

Aneurysmal SAH follows the rupture of an intracranial aneurysm, which is an acquired focal abnormal dilation of the wall of an artery in the brain. Such a vascular malformation is most commonly located at branching points of the major arteries at the base of the brain. Although once thought to be congenital, saccular aneurysms are now regarded as an acquired, hemodynamically-induced injury to the vascular wall. According to the size, aneurysms can be classified as small (2–7 mm in diameter), medium (7–12 mm in diameter), large (13–24 mm in diameter), and giant (>25 mm in diameter).[1]

SAH can also be associated with heritable connective tissue diseases and the familial occurrence, thus supporting for a genetic factor. Among these, autosomal dominant polycystic kidney disease (ADPKD), which is found in only 2% of all patients with SAH.[83] Other genetically determined disorders associated with SAH are Ehlers–Danlos syndrome type IV, neurofibromatosis type 1, and Marfan syndrome.

All population studies have clearly shown that cigarette smoking confers a predisposition to aneurysmal SAH[9,43,48,74] whereas moderate-to-high level alcohol consumption is an independent risk factor.[43] Finally, the risk is not so far clear regarding the use of oral contraceptives[42] and hormone replacement therapy.[94]

Clinical presentation

The classical clinical presentation of SAH is characterized by a sudden and explosive headache never felt in the patient's clinical history. Usually, a loss of consciousness occurs in almost half the patients and focal neurological signs develop afterward in one-third of the cases.[35,56]

Following the bleeding, the intracranial pressure rises to reach the mean arterial pressure, thus dropping the cerebral perfusion pressure and explaining the transient or persisting decreased consciousness that can occur. The severity of the hemorrhage and its effects on intracranial pressure ultimately determine the severity of the presenting symptoms.

In these patients, diagnosis is easy to perform and neuroradiological investigations can be readily undertaken. In patients in whom a headache is the only symptom, it is harder to make a firm diagnosis because other pathologies, such as innocuous forms of headaches, can present with the same clinical presentation. In these cases, hospital consultation should be required. Although we do know that an explosive headache is the only symptom of aneurysmal SAH in only 10%,[58] a medical approach can avoid disastrous consequences.[95]

Patients sometimes report an unusual headache several weeks prior, which may represent a minor leak of blood

into the wall of an aneurysm or the subarachnoid space.[54] In some cases, the severity of the headache can be quite mild and misleading. Accordingly, in every patient complaining of a new headache, SAH should be considered and investigated.

In cases without a sudden headache, other symptoms can be presented. In this regard, seizures can be the presenting symptoms of SAH in approximately 6–16% of patients.[77] In 1–2% of the patients, an acute confusional state can be observed, and in most such patients a history of a sudden headache is lacking.[81] In such patients, neuroradiological investigations can provide the diagnosis of aneurysmal SAH.

Overall, in a ruptured aneurysm, the clinical status depends on the severity and location of the SAH, and the neurological examination can suggest indications of the cause of SAH. For instance, in a case of a posterior communicating artery aneurysm, often a third nerve palsy with pupillary dysfunction is found. Following SAH, there may be nuchal rigidity and intraocular hemorrhage although their occurrence does not correlate with aneurysm location. The neurological exam may be normal, show focal neurological signs due to a local mass effect from a hematoma, or the patient may be in a deep coma with decerebrate rigidity.

Investigations

When an aneurysmal SAH is clinically suspected, computed tomography (CT) scanning is the examination of choice because it can identify the hyperdense signal provided by the extravasated blood in the basal cisterns. Often, the location and spreading of the bleeding can suggest the location of the ruptured aneurysm. A false-negative diagnosis of SAH on CT is possible because studies can be negative in ~ 2% of the patients with SAH.[100]

Lumbar puncture can be still an indispensable tool for SAH diagnosis in patients with a convincing clinical history and negative brain imaging. In case of an SAH, a lumbar puncture performed at least 12 h following the clinical presentation gives the cerebrospinal fluid a yellow tint after centrifugation (xanthochromia), resulting from the breakdown products of hemoglobin.

A patient suspected of having a ruptured aneurysm should undergo cerebral angiography that can describe the causative aneurysm and direct appropriate definitive management. Conventional cerebral angiography, including three-dimensional reconstructions, allows for better characterization of the morphology, orientation, neck size, adjacent vessels, and any additional aneurysm. However, CT angiography is an alternative investigation with high accuracy and increased sensitivity in diagnosing cerebral aneurysms.[65] CT angiography can be quickly performed and guide the decision-making process. A recent meta-analysis has suggested that CT angiography can be used as a primary examination in patients with SAH,[106] although such an investigation has shown to be weak in the detection of small aneurysms and those adjacent to the skull base.[40,45,70] Therefore, if CTA does not detect a source of SAH, digital subtraction angiography generally is indicated. This is stated in the American Heart Association/American Stroke Association guidelines for the management of aneurysmal SAH, which strongly recommend DSA in their class I recommendations.[7]

Treatment approach

The primary goal of treatment is to exclude the aneurysm sac from the intracranial circulation while preserving the parent artery. In unruptured aneurysms, the decision as to whether to treat or observe the malformation is made on a case-by-case basis. In this regard, the natural history must be carefully evaluated. The International Study of Unruptured Intracranial Aneurysm (ISUIA) have suggested that aneurysm size and location were independent predictors for aneurysm rupture.[108] ISUIA examined 1692 patients with cerebral aneurysms with a mean follow-up of 4.1 years. Rupture rates differed depending on the size and location, ranging from 0% in aneurysms less than 7 mm located in the internal carotid artery, anterior circulation, or middle cerebral artery to up to 50% in aneurysms greater than 25 mm in size located in the posterior circulation.[108] Most recently, the Unruptured Cerebral Aneurysm Study (UCAS) yielded results similar to the ISUIA.[38] However, several investigators have contradicted these studies, reporting a higher percentage of small aneurysms among their case series of ruptured intracranial aneurysms.[44,105,109] This indicates a discrepancy between the ISUIA and UCAS data and the size of ruptured aneurysms seen in routine clinical practice. The conclusions reported from ISUIA have stimulated many controversies because they were based on data-driven post-hoc reconstructions of artificial subgroups too small to be reliable. For instance, in agreement with the study, aneurysms less than 5 mm would not rupture, and therefore should not be considered for treatment. This message, in our opinion, is misleading because it would exclude these patients from proper treatment. The natural history of these aneurysms remains unpredictable with the potential to increase in size, change in configuration, and bleeding rate that appears to be uncertain compared to larger aneurysms. Although ISUIA is the largest prospective study on unruptured aneurysms, it is actually quite small when one considers the ambitions of the study, the retention of patients and length of follow-ups, and the intention to analyze numerous subgroups. Accordingly, the conclusions made about aneurysm size in relation to rupture rate are still open to question.

For ruptured cerebral aneurysms, it is well-known that the exclusion of the vascular malformation from the cerebral circulation should be performed as soon as

possible.[7] In this scenario, both surgical clipping and endovascular techniques are valid treatment modalities to achieve such a goal. Three main randomized, prospective studies have compared both techniques.[49,50,64,66-69,88,89,101] Among these, the International Subarachnoid Aneurysm Trial (ISAT) have strongly modified the management of ruptured cerebral aneurysm because it reported an improved survival with coiling, which was statistically significant when compared with surgical treatment at 12 months follow-up.[69] Although the rate of occlusion was higher in clipped aneurysms (82%) as compared to coiled aneurysms (66%), coiling resulted in a significantly decreased rate of death or dependency as compared to clipping. Despite the results of this study stimulated a number of criticisms, the treatment of ruptured cerebral aneurysms is dramatically changed over the years being, to date, the endovascular treatment the approach chosen for most ruptured intracranial aneurysms. Further investigations, however, are needed to assess the long-term effectiveness of the endovascular techniques.

Although advances have occurred in the endovascular treatment of intracranial aneurysms, microsurgery remains an important technique for managing many aneurysms including those which fail endovascular treatment.[4] In this regard, the evidence for microsurgical retreatment of previously coiled intracranial aneurysms is sparse, and guidelines are lacking. Indications for retreatment include incomplete obliteration and subsequent growth of residual neck or dome. It should be considered that the necessity for future retreatment and the additional complexity afforded by the presence of a coil mass in these locations[24] should warrant reconsideration of the reflex notion that endovascular coiling is preferable to microsurgical clipping for lesions in certain anatomic locations.

CURRENT SUPPORTIVE CARE FOR SUBARACHNOID HEMORRHAGE

Outcome following aneurysmal SAH depends on several factors, of which the severity of the initial hemorrhage and the patient age are the most important aspects. Other factors, however, can be considered, such as rebleeding occurrence and timing and technical success of the aneurysm treatment. While aneurysm closure is the primary concern in all patients with aneurysmal SAH, the contribution of perioperative medical management is considerable. The first 2 weeks following SAH is the peak period for morbidity and mortality due to the injury from the initial hemorrhage, vasospasm, cerebral ischemia, and rebleeding. Accordingly, prevention of the rebleeding and optimization of the medical management to counteract the cerebrovascular dysfunction following SAH can result in significant benefits to the patient.

SAH-related cerebral ischemia is one of the critical issues. It occurs in 30% of the patients between days 4 and 10 following aneurysm bleeding.[82] Because of its delayed onset, this complication is called delayed cerebral ischemia (DCI).[16] Although many other terms are still used in the literature.[103] It presents with focal neurological deficits or alteration in the level of consciousness, often with fluctuating pattern. Signs of cerebral ischemia can be reversible but may also progress to cerebral infarction, thus resulting in severe disability or death.[79] These clinical deficits can occur along with angiographic evidence of vessel narrowing. Such an occurrence, therefore, has contributed to the interchangeable use of the terms for DCI and angiographic vasospasm, although each may occur independently. Accordingly, it has been proposed to reserve the term "vasospasm" for angiographic arterial narrowing.[103]

Cerebral vasospasm occurs in 70% of the patients following aneurysmal SAH and leads to symptomatic brain ischemia in 30% of the cases.[8] The most critical aspect is the lack of effective treatments. Pharmacological interventions have been assessed in experimental studies and clinical trials with only partial success.[26] Although a number of researchers have been performed, the pathogenesis of secondary cerebral ischemia following SAH has not been completely clarified. It is generally accepted that, after the hemorrhage, a cascade is activated by factors released into the subarachnoid space, which induces vasoconstriction of the main arteries and thereby secondary ischemia. It has been suggested that the pathogenesis of delayed cerebral vasospasm is related to a number of pathological processes, including endothelial damage and smooth muscle cell contraction resulting from spasmogenic substances generated during lysis of subarachnoid blood clots,[39] changes in vascular responsiveness, and inflammatory or immunological reactions of the vascular wall.[92] Some progress, however, has been made in the prevention of secondary ischemia after aneurysmal SAH by changes in general medical approach as well as by specific drug treatment. The main therapeutic interventions used are limited to manipulation of systemic blood pressure. In general, intravascular volume management should prophylactically target euvolemia with the utilization of an isotonic crystalloid as the preferred fluid for volume replacement.[15] In this regard, there is a revised recommendation for the use of euvolemic-induced hypertension rather than triple-H therapy as the primary method for treatment of most patients with cerebral vasospasm.[5,15]

Finally, the recent trial on the effects of induced hypertension on cerebral perfusion in DCI after aneurysmal subarachnoid hemorrhage did not show significant differences in change in overall CBF between treated and untreated patients.[20]

Furthermore, calcium-channel blockade with nimodipine is given to all patients. The role of oral nimodipine in the

prevention or treatment of delayed ischemic events has been exhaustively reviewed.[93] Most reports confirm that the incidence of severe neurological deficits is reduced, despite evidence suggesting that there is little effect on the incidence and severity of angiographic vasospasm.[75,76] Anti-ischemic effects of nimodipine and nicardipine may occur by inhibiting calcium entry into smooth muscle cells and vasoactive substance release from platelets and endothelial cells. In addition, calcium antagonists may favor the development of collateral circulation.[76] They also may be neuroprotective.

The largest randomized multicenter double-blind placebo-controlled study of nimodipine evaluated 554 patients with SAH. Within 96 hours following the bleeding, compared to placebo, nimodipine significantly reduced cerebral infarction and poor outcomes. It also showed a reducing rebleeding rate. Overall, in nimodipine-treated patients, a reduction in death and disability was observed.[75]

Nimodipine, administered orally at a dose of 60 mg every 4 h and maintained for 3 weeks, usually is well tolerated, even if its use might be associated with systemic hypotension especially when intravenously administered.[15]

EMERGING THERAPIES

Several medical treatments have been investigated to prevent or reverse cerebral vasospasm following SAH, including calcium channel blockers, statins, endothelial receptor antagonists, magnesium, erythropoietin, and others.[2] However, definitive therapeutic recommendations are difficult to endorse because high levels of evidence are lacking.

Magnesium

Several clinical studies have investigated the effects of magnesium on cerebral vasospasm and neurological outcomes in patients with aneurysmal SAH.[10,71,98,104,107,110] The use of magnesium following SAH is based on its action as a noncompetitive calcium antagonist via binding to voltage-dependent calcium channels. Considering its mechanism of action and the knowledge that following SAH hypomagnesemia occurs in more than 50% of the patients,[97] often associated with a poor outcome, magnesium has been investigated as a possible neuroprotective agent. Several preclinical studies have demonstrated that magnesium can provide vasodilation by inhibiting the cellular calcium influx, inhibiting vascular smooth muscle contraction, and decreasing glutamate release.[91,99]

Although preclinical and phase II studies have shown promising results, a recent multicenter phase III randomized placebo-controlled study assessing the clinical efficacy of intravenous administration of magnesium following SAH failed to demonstrate a clear benefit.[112] In this study, 327 patients with SAH within 48 hours of hemorrhage onset were enrolled. The primary outcome was a favorable neurological outcome at 6 months. The investigators did not find significant differences between the magnesium and placebo groups as the percentage of favorable outcome at 6 months was similar in both the groups. Even the occurrence of vasospasm was comparable in both the groups. The disappointing results of this clinical trial have been confirmed by subsequent clinical investigation.[55] Accordingly, the current recommendation is to administer magnesium as necessary to prevent hypomagnesium in SAH-affected patients.[18]

Statins

In the last 10 years, an increasing number of evidence has shown the potential benefits of statins in the setting of SAH-induced cerebral vasospasm.[59]

Cerebral arterial blood vessel tone is balanced by vasoconstrictor and dilator systems designed to achieve equilibrium, depending on several factors. It is widely accepted that it is able to modulate vascular smooth muscle function through the release of endothelial-derived relaxing factors (EDRFs), the most important substance being nitric oxide.[19] On the other hand, endothelial cells also produce vasoconstrictor substances, the so-called endothelial-derived contracting factors (EDCFs), the most potent being the peptide endothelin.[19] In physiological conditions, there is a balance between vasodilator and constrictor mechanisms in the control of the cerebrovascular tone. It has been suggested that statins upregulate endothelial nitric oxide synthase and the availability of endogenous nitric oxide by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. By this mechanism, statins would correct the imbalance between the nitric oxide and endothelin pathways, which is believed to be a main contributor to the pathophysiology of cerebral vasospasm.[78] Furthermore, statins could provide a neuroprotective action by decreasing the glutamate-mediated excitotoxicity, reducing the production of reactive oxygen species, and modulating the inflammatory response.[17]

Unfortunately, translation of preclinical studies has provided basically negative clinical results.[59] Although a phase II randomized placebo-controlled trial in SAH patients has shown that pravastatin was able to decrease the incidence of severe vasospasm, delay cerebral ischemia and mortality, a subsequent phase II randomized, double-blind, placebo-controlled study did not show significant differences in the outcome between simvastatin and placebo-treated patients.[102]

The recent results of the Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) study did not detect any benefit in the use of simvastatin for long-term or short-term outcome in patients with aneurysmal SAH.[47]

Endothelin receptor antagonists

Endothelin receptor antagonists have been found to be effective in reducing the incidence of vasospasm following aneurysmal SAH.[113] These agents can inhibit the binding of one potent vasoconstrictor, endothelin-1, to its receptors on vascular smooth muscle cells.

Endothelin belongs to a family of three isopeptides with common structural features (ET-1, ET-2, ET-3). ET-1 has a more marked effect on cerebral arteries than do the other two isoforms and has been reported to play an important role in the pathogenesis of SAH-related vasospasm because it is able to cause a dose-dependent and long-lasting vasoconstriction.[37] Endothelins act by at least three different receptor subtypes, the ETA receptor, which is localized in vascular smooth muscle cells and mediates vasoconstriction and two different ETB receptor subtypes. The ETB1 receptor subtype is present in vascular endothelial cells and mediates the endothelium-dependent vasodilation.[80] The ETB2 receptor subtype is present in smooth muscle cells causing vasoconstriction.[14] The well-documented effects of endothelins on cerebral vessels suggest that they are strongly involved in cerebral vasospasm. A number of experimental studies convincingly demonstrate the preventive and/or therapeutic potentials of endothelin receptor antagonists.[111]

Among the number of molecules investigated, Clazosentan, a selective ET-1 receptor antagonist, has shown efficacy in preclinical and clinical studies.[60] An early phase II study of clazosentan (CONSCIOUS-1) demonstrated that clazosentan produced dose-dependent reductions in angiographic vasospasm.[60] Subsequently, 2 phase III studies were conducted to evaluate clazosentan compared to placebo (CONSCIOUS-2 and CONSCIOUS-3)[61-63] in mortality, vasospasm-related cerebral infarcts, and delayed ischemic neurological deficit. In the CONSCIOUS-2 study, poor functional outcomes occurred more frequently in the clazosentan-treated patients, whereas the mortality between the groups was the same. Furthermore, the occurrence of adverse events in the clazosentan group (i.e., pulmonary edema, hypotension, cerebrovascular spasm, pleural effusion, and cerebral infarction) halted the study and prevented the CONSCIOUS-3 to be further continued.[61]

Tirilizad

Free radical-induced lipid peroxidation has been found to play a critical role in vasospasm and in the cascade of ischemic cell death.[33] Tirilizad is a nonglucocorticoid 21-aminosteroid that functions as a free radical scavenger by inhibiting lipid peroxidation. This antioxidant effect is believed to provide neuroprotection also during SAH.

An initial phase II clinical study has shown that tirilizad can reduce angiographic vasospasm following SAH.[31] Subsequently, additional clinical studies were conducted.[32,46,52] However, these studies demonstrate conflicting results regarding the effect provided by tirilizad. Although it has been shown to reduce the frequency of secondary symptomatic vasospasm in patients with aneurysmal SAH, its role in the incidence of cerebral infarction as the result of symptomatic vasospasm still remains unresolved. Tirilizad can be administered without risk of cardiovascular and mental adverse effects. The most common adverse event of tirilizad reported was phlebitis.[52]

Erythropoietin

Erythropoietin is a 165 amino acid (~30 kDa) glycoprotein, member of the type I cytokine superfamily, which regulates the differentiation and proliferation of immature erythroid cells.[41]

At the beginning, erythropoietin was well-known for its function in maintaining the tissue oxygenation by regulating the number of erythrocytes in a negative-feedback control system that operates between the kidney and the bone marrow. The discovery that it has biological functions apart from regulating erythropoiesis was unexpected and supported by numerous studies. Substantial evidence has indicated that erythropoietin mediates neuroprotective effects by different mechanisms of action including maintaining normal vascular autoregulation, which has clinical relevance in aneurysmal SAH. In preclinical studies, erythropoietin has shown to reduce the mortality rate, improve functional outcome, and prevent brain ischemic damage following experimental SAH.[3,13,21-23,25-30] Based on these preliminary results, clinical trials blossomed, with uncertain results.[90,96] The first clinical trial was preliminarily terminated, with unpredictable results, because of a lower than expected inclusion rate.[90] A recent phase II, proof-of-concept trial tested the hypothesis that acute systemic erythropoietin therapy in patients following aneurysmal SAH can reduce cerebral vasospasm and shorten impaired autoregulation as primary endpoints, which subsequently decrease delayed ischemic deficits (DIDs) and improve clinical outcome as secondary endpoints.[96] As a result, although no differences were demonstrated in the incidence of vasospasm and adverse events between the two groups, patients receiving erythropoietin had a decreased incidence of severe vasospasm, reduced DIDs, a shortened duration of impaired autoregulation, and more favorable outcome at discharge.

Despite some limitations, such as small number of cases, a single erythropoietin dose, a single center, lack of scheduled CT scan examinations, this study confirmed a potential effective action of erythropoietin in limiting cerebral vasospasm and ischemia after aneurysmal SAH.[30]

Potential adverse effects, however, should be considered. Several lines of evidence suggest that chronic

erythropoietin administration can produce hypertension, hypertensive encephalopathy, accelerated atherosclerosis, seizures, and thrombotic/vascular events.[21] In a recent prospective, randomized, double-blind, placebo-controlled trial, the safety of a single intravenous bolus of epoetin alfa in patients with acute ST-segment elevation myocardial infarction (STEMI) was associated with higher rates of adverse cardiovascular events among older patients.[72]

Finally, the dosage used in the clinical setting is the lowest dose considered to be effective following SAH. It can be argued that uncertain results from the first clinical trial[90] and the weak findings of the second clinical study[96] can find answers in the low dosage used and frequency of treatment. Results from future clinical studies will provide further evidence regarding the use of erythropoietin after SAH.

Glyburide

Glyburide is an oral anti-diabetic drug that has recently shown neuroprotective properties.[85] It has been pointed out that glyburide can act through the inhibition of SUR1, a membrane protein that co-associates with heterologous pore-forming subunits to form ion channels.[87] Following injury in neurons and endothelium, SUR1 binds with an ATP- and Ca2+-sensitive nonselective cation-channel, known as transient receptor potential melastatin 4 (Trpm4), to form Sur1-Trpm4 channels.[87] Opening of SUR1-Trpm4 channels is associated with excess influx of Na+, which is accompanied by influx of Cl− and H_2O, resulting in cytotoxic edema or cell death.[85] In microvascular endothelium, such mechanisms can result in the formation of ionic and vasogenic edema.

In an SAH rat model and human tissue, SUR1 blockade by glyburide has been associated with a significant reduction in several markers of neuroinflammation.[86] Furthermore, Sur1-Trpm4 channels were upregulated in humans and rats with SAH. In rats, glyburide administration reduced SAH-induced immunoglobulin G extravasation and TNFα overexpression. In addition, inhibiting SUR1 by using low dose glyburide after SAH resulted in a significant attenuation in the SAH-induced alteration in barrier permeability and inhibition of caspase-3 activation.[86]

Recently, patients with type 2 diabetes affected by ischemic stroke and taking a sulfonylurea drug for glycemic control presented with significantly fewer deaths and a significantly lower rate of symptomatic hemorrhagic transformation.[51] These findings have been recently confirmed by the preliminary results of a multicenter, randomized, double-blind, phase II trial that examined the efficacy of glyburide in the prevention of malignant edema in severe anterior circulation ischemic stroke.[84]

Although animal models support the possible neuroprotective role of glyburide in aneurysmal SAH, future clinical trials would reveal the efficacy of this drug in this setting.

CONCLUSIONS

Aneurysmal SAH is a critical neurological disease. Pharmacotherapy has an established role in several aspects of aneurysmal SAH. Upon the closure of the cerebral aneurysm, the primary concern is the prevention and treatment of the cerebrovascular dysfunction following the bleeding. Though a number of agents have been evaluated, there has been very limited success. Several compounds have been demonstrated to be effective in preclinical models, while only a part of these have entered clinical development, and some of those that survived early safety trials have been studied in controlled efficacy trials. Despite these efforts, all phase III trials have so far failed in demonstrating efficacy of these agents. The pathophysiological heterogeneity of SAH-affected patients, the absence of satisfactory pharmacokinetic investigations necessary to assess optimal doses, and the timing for administration may have led to the clinical trial failures. Because experimental models of SAH are designed to produce a relatively homogeneous type of injury, they may not be able to adequately reproduce all the aspects that are observed in human SAH. This may in part explain why drugs that showed promise in preclinical studies failed in clinical translation. SAH is continuing to prove to be a critical multifactorial condition that involves complex interactions between pathological mechanisms. A greater understanding of the pathology of SAH will allow for more efficient translation from preclinical models into therapeutic advances for patients.

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Conflicts of interest

There are no conflicts of interest.

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