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SPECIAL ARTICLE

Management of cerebral vasospasm in subarachnoid hemorrhage

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ABSTRACT

Subarachnoid hemorrhage (SAH) has been shown to result in cerebral vasospasm at day 4 to day 14, which is the main cause of mortality and morbidity after SAH. Outcome after SAH depends on many factors, including the severity of the event, medical management, and prevention of several serious complications. The principal goal in management of vasospasm after SAH is to prevent delayed ischemic neurological deficit (DIND) by decreasing intracranial pressure (ICP), optimizing cerebral oxygen demand rate and improving cerebral blood flow (CBF). Therapeutic management has been applied to prevent or treat vasospasm, including hemodynamic therapy, and endovascular therapy. Endovascular therapies, including mechanical angioplasty and chemical angioplasty with administration of intra-arterial (IA) vasodilator, have been widely used and given a good outcome. The purpose of this article is to describe the management of vasospasm including medical management and endovascular treatment. This review will describe the treatment modalities and management strategies to treat vasospasm.

Key words: Subarachnoid hemorrhage; Cerebral vasospasm; Management vasospasm

Abbreviations: SAH – subarachnoid hemorrhage; aSAH – aneurysmal subarachnoid hemorrhage; TCD – transcranial Doppler; ROS – reactive oxygen species; ICAM – intercellular adhesion molecule; VCAM – vascular cell adhesion molecule; IL – interleukin; CTA – computed tomography angiography; MRA – magnetic resonance angiography; CBF – cerebral blood flow; DIND – delayed ischemic neurological deficit; RCT - randomized controlled trials

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INTRODUCTION

Cerebral vasospasm following subarachnoid hemorrhage (SAH) was first introduced in 1951 by Ecker and Riemenschneider.[2] SAH is closely related to 40% of mortality in patients and may result into vasospasm that can lead to delayed cerebral ischemia.[1] Vasospasm is the main cause of mortality and morbidity after SAH.[2] About 67% of aneurysmal subarachnoid hemorrhage (aSAH) will result into vasospasm and 10-45% of vasospasm victims will develop infarct.[1] Angiographic vasospasm occurs in 70% and clinical vasospasm in about 40% of SAH patients. About 30% of the patients with clinical vasospasm will develop a delayed ischemic neurological deficit (DIND) and suffer from mortality or severe deficits.[2] Vasospasm is a focal or diffuse narrowing of vessel caliber because of smooth muscle contraction in the arterial wall, and could be detected by angiography or imaging studies such as MRI, CT or transcranial Doppler (TCD).[3]

PATHOGENESIS

Vasospasm is a serious condition caused by constriction of the blood vessels.[2] This condition is related to proliferation of myofibroblast, hyperplasia of intimal smooth muscles, deposition of collagen and fibrosis.[2] The biomechanics and the role of inflammation remains incompletely understood.[3] There is an association between the amount of subarachnoid blood in brain imaging and the severity

of vasospasm as recognized by Fisher scale.[4] It has been described that products of blood degradation will trigger a cascade of molecular changes resulting into vasospasm.[4]

After hemorrhage, there is a continued process of increase in scavengers, nitric oxide, and reactive oxygen species (ROS) and also increase in the vasoconstrictor mediators such as thromboxane A2, ET-1, thrombin, and serotonin which results in vascular mechanics leading to vasoconstriction.[3] Clot-associated mitogens such as platelet derived growth factor, ET-1, and growth factor B transformation will initiate the smooth muscle cell and adventitial fibroblast proliferation and migration, and all these changes will promote additional collagen synthesis, increasing the structural stiffness and the vessel wall thickness.[3] Release of IL-1, IL-6, IL-8, and TNF-α in inflammatory response will upregulate the chemotactic factors such as intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM).[3]

Severe vasospasm could cause disruption of endothelial cells, promote decreased nitric oxide and prostacyclin endothelial cell production. This process decreases vasodilator circulating responsiveness and further initiates constriction of blood vessels.[3] Despite of inflammatory and biomechanics roles, some genetic factors have also been associated with vasospasm. Several genes have important role in vasospasm such as eNOS, Hp, CBS, ApoE, PAI-1, and RyR1.[3]

Vasospasm occurs from 4th day to 14th day, following aSAH. The peak of incidence occurs on day 6th to 10th.[2] The vessels that are most frequently affected are located in the circle of Willis.[2] This vasospasm will decrease CBF and the final effect is DIND.[2] Some important predictors of vasospasm include density and volume of blood, and prolonged duration of SAH.[2]

DIAGNOSIS

Vasospasm has been divided into symptomatic and angiographic vasospasm.[3] In symptomatic vasospasm symptoms are more objectively explained by new focal deficits and not by rebleeding or hydrocephalic conditions.[3] Clinicians need to beware of newly developed neurological deficit, increase in mean arterial blood pressure, other mild symptoms e.g. rise of temperature, worsening progressive headache, neck stiffness, or progressive hyponatremia.[3] Symptomatic vasospasm rarely occurs within 3 days after SAH, with the peak at day 8. 4% of symptomatic vasospasm occurs after 13th day.[3] Fisher grading scale has been widely used to predict vasospasm.[3]

Angiographic vasospasm occurs in 48 hours after SAH.[3] About 30-70% occur at day 3 to day 5 after SAH, maximal vasospasm is noted at day 5 to day 14 and gets resolved 2 to 4 weeks after SAH.[6] Supporting tests are needed to evaluate the vessel caliber to detect vasospasm such as transcranial Doppler study (TCD), and imaging perfusion with magnetic resonance angiography (MRA), computed tomography angiography (CTA) etc.[3] Perfusion imaging can be useful to detect brain ischemia area, this is a new recommendation in AHA/ASA guidelines in 2012 (class IIa, level of evidence B).[7]

TCD was introduced by Aaslid in 1982 for detection of vasospasm.[3] Some advantages of TCD are; it can be performed at bedside with a portable device, is specific to detect vascular narrowing, can be repeated as necessary as needed, no side effect, is cheaper and noninvasive.[3] TCD assesses direction and blood flow velocity in proximal site of cerebral arteries through trans-temporal acoustic window.[3] Limitations of TCD are; a sensitivity of less than 60%, operator dependent, and needs a good acoustic window.[3]

TCD is reasonable to detect vasospasm, this is a new recommendation from AHA/ASA guidelines in 2012 (class IIa, level of evidence B).[7] Based on American Academy of Neurology expert committee, TCD can detect severe vasospasm is level A, class II level of evidence.[3] The normal value of middle cerebral artery mean flow velocity is 62 ± 12 cm/sec, if there is a significant spasm in angiogram, the mean flow velocity become 120 cm/sec, and mean flow velocity up to 200 cm/sec related to severe vasospasm and up to 50% narrowing on angiogram.[3]

CTA imaging has widely been used for measured vasospasm.[3] It was first used for detecting vasospasm in 1997 by Ochi et al., they demonstrated in two cases that vasospasm was correctly identified, and it was confirmed with angiography catheter.[3] CTA is an examination without limitation for imaging the anatomy like TCD, and offers rapid imaging reconstruction.[3] CTA has 79.6% sensitivity and 93.1 % specificity.[3] The gold standard for diagnosing vasospasm is the catheter-based angiography.[3] Cerebral digital substraction angiography is gold standard to diagnose angiographic vasospasm by vessel caliber and calculation of transit time.[5] There are several limitations and disadvantages of this procedure, such as iodine contrast and radiation exposure, iatrogenic stroke risk, catheter induced vascular injury, and finally it is experienced operator dependent.[5]

MEDICAL THERAPY OF VASOSPASM

The main purpose of therapy is to maximize CBF to the brain to prevent DIND, to reduce demand by decreasing cerebral metabolism, and prevent secondary injury from cerebral ischemia or other condition such as hydrocephalus.[2,3] The management options include administration of oral calcium channel blockers and fluid therapy to preserve the hemodynamics; and also endovascular therapy.[2] Angiography catheter is used as a gold standard to diagnose vasospasm, and it is also used as a route to perform rapid endovascular treatment of DIND following SAH. Early aggressive endovascular therapy is still reasonable in case there is suspicion of vasospasm with secondary neurological deficit, or when even after optimizing hemodynamics there is no improvement.[3]

1. Hemodynamic Therapy

Hemodynamic therapy, also known as triple H therapy, is one of the symptomatic management strategy.[3] It includes hypertension, hemodilution, and hypervolemia widely known and used as a vasospasm management, but there is no significant changes in prognosis.[2] One of randomized controlled trials (RCT) showed that there was no good evidence that triple H management improved clinical outcome in SAH patient or in CBF.[2] The other RCT evaluated normovolemia compared with prophylactic hypervolemia and there was no outcome improvement and no decrease in delayed ischemia in the prophylactic hypervolemia group, and no difference in CBF despite increasing the cardiac filling pressure.[3]

Aggressive hypertension and induced hypertension are commonly used although there is no sound evidence to support it.[3] Based on AHA/ASA guidelines in 2012 induced hypertension is recommended for delayed ischemic injury, unless blood pressure is increased at baseline or cardiac status precludes it (class I, level of evidence B).

Hemodilution is still controversial, there is strong evidence that hemodilution increases CBV but results in a decreased capacity of oxygen delivery with isovolemic hemodilution.[3] There is no reliable data about how much hematocrit value is desirable in vasospasm treatment, some studies describe 28% to 32% hematocrit to be advisable for this purpose.[3] Triple H therapy has been related to significantly increased risks, such as brain edema, electrolyte imbalance, heart failure and potential risk of rupture of unsecured aneurysm.[2] Preventing potential irreversible ischemic damage is important to aggressively manage metabolic and systemic problems, such as electrolyte imbalance, acidosis, hypoxia, hyperglycemia, hyperthermia, and potential septic episode.[6] Based on AHA/ASA guidelines in 2012 prophylactic hypervolemia or balloon angioplasty procedure before angiographic vasospasm seen is not recommended (new recommendation, class III, level of evidence B).[7] Hyponatremia is independent risk factor for poor outcome because it results in cerebral salt wasting and promote volume contraction. Treatment includes correcting hyponatremia with hypertonic saline and fludrocortisone and administration of isotonic fluids.[3]

2. Oral and Intravenous (IV) Therapy

a. Nimodipine

Nimodipine is group of dihydropyridine that avoids calcium channels voltage-gate and has vasodilator effect at arterial smooth muscle.[8] Nimodipine was approved by FDA as a drug for vasospasm treatment with a half-life of 9 hours.[8] Nimodipine oral can significantly improve neurological outcome in SAH patient, but the underlying mechanism is still uncertain.[2,3] There is some evidence that nimodipine can reduce incidence of cerebral infarction and increase improvement outcome in vasospasm after SAH.[2] Oral nimodipine can decrease incidence of vasospasm-induced cerebral infarction by about 34% and 40%.[2] Nimodipine oral should be administrated in all SAH patients (class I, level of evidence A).[7] Nimodipine has been known to improve the neurological outcome but not cerebral vasospasm.[7]

The dose of oral nimodipine is 60 mg every four hours for 3 weeks, although related to systemic hypotension especially when administrated IV.[9] Some literature describe the other dosage such as 30 mg nimodipine orally every 2 hours in low blood pressure.[8] A retrospective cohort study assessed nonstandard dosing of nimodipine (30 mg every two hours). A total of 166 patients were given 60 mg nimodipine every 4 hours initially, 49 % patients (81 patients) were changed to nimodipine 30 mg every two hours and 51% (85 patients) continued 60 mg nimodipine every four hours. This study showed that blood pressure related factors such as vasospasm incidence and need for vasopressors were correlated to patients being switched to the nonstandard regimen. Future studies are still needed to decide whether the nonstandard regimen (30 mg nimodipine every 2 hours) is safe and effective for aneurysmal subarachnoid hemorrhage patients.[10]

b. Nicardipine

Nicardipine belongs to the group of dihydropyridine

– the potent antihypertensive therapy. It selectively inhibits calcium ions in smooth muscle.[8] Due to its selective action at cerebrovascular smooth muscle, it can be used as vasospasm therapy after SAH.[8] Although some earlier studies described that administration of nicardipine was related to poor outcome and mortality in vasospasm patients.[8]

An RCT found that administration of high dose nicardipine in 0.15 mg/kg/h infusion related to a decrease in clinical and angiographic vasospasm in TCD findings, but overall nicardipine efficacy was still limited.[2] Another RCT found low dose nicardipine 0.075 mg/kg/h also gave benefits in vasospasm and with lower side effects.[2] A meta-analysis assessed effectiveness of nicardipine to avoid vasospasm in aSAH. This study found nicardipine infusion decreases mortality and risk of bad outcome include death, dependency, and vegetative state with odd ratio 0.45 (95% CI 0.15-1.29) and 0.58 (95% CI 0.37-0.90).[11]

d. Statins

There was evidence about potential benefits of statins in SAH induced vasospasm.[9] Some centers have been using statins for vasospasm management but the effect remains controversial.[2] Statins upregulate synthesis of endothelial nitric oxide and inhibition of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase related to availability of endogenous nitric oxide. With regard to this mechanism, statins can correct imbalance between endothelin pathways and nitric oxide that is believed to be role contributor of vasospasm.[9] The other effect of statins is neuroprotection by decreasing glutamate-mediated excitotoxicity, modulating the response of inflammatory, and decreasing of ROS production.[9] Statins also improve CBF and impair autoregulation.[12] Statins needs 24 hours to increase CBF in ischemic brain regions.[12]

Unfortunately, a large study Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) has not shown any advantage for long or short term statin use in outcome.[12] Six RCT's consisting of 249 patients found that there was no significant decrease in vasospasm and incidence of poor neurological outcome. However, there was significant difference in DIND and mortality. From this study it was concluded that statins may have beneficial effects in prevention of mortality in aSAH but are not considered for standard therapy.[13] Other RCT and observational studies evaluated the statins efficacy in aSAH patients and the measured outcome included delayed cerebral ischemia, cerebral vasospasm, and bad outcome. There were a total 1031 patients in six RCT's consisted of 504 patients, who received statin therapy and 527 patients in placebo group . The results showed no benefit of statins in aSAH.[14]

A cohort study in Korea assessed high dose simvastatin in vasospasm and clinical outcome after SAH. The 99 subjects were divided into 3 groups that received 20, 40, and 80 mg simvastatin. Primary outcome was symptomatic vasospasm incidence, and clinical outcome measured after 1 month and 3 months with mRS score. The results; 36.4% symptomatic vasospasm in 20 mg simvastatin group, 8.8% in 40 mg simvastatin group, and 3.2% in 80 mg simvastatin group. Clinical outcome was not significantly different in three groups. The study concluded taht 80 mg simvastatin therapy was effective to prevent cerebral vasospasm after aSAH but did not improve clinical outcome.[15]

e. Magnesium Sulfate

Magnesium sulfate is widely used in pre-eclamptic pregnancy to decrease contraction of uterine smooth muscle.[8] Mechanism of action is non-competitive calcium antagonism with neuroprotective effects.[8] It has vasodilator action by avoiding voltage-dependent calcium channels and reducing glutamate release.[8] It is reasonable to maintain the normal value of magnesium, but the administration of continuous magnesium infusion was still not supported by evidence.[8] A meta-analysis evaluated the efficacy of magnesium at different times within 24 hours after SAH. This study found no beneficial effect of magnesium in poor outcome or delayed cerebral ischemia.[16] Therefore, further studies to evaluate its clinical effect, ideal dosage and side effects are needed.[8]

3. INTRACISTERNAL THERAPY

Intracisternal vasoactive therapy such as nicardipine, milrinone, and papaverine have been studied and have shown promising results in *in vivo* and *in vitro* studies, but still limited effect in a human study.[3] Administration of thrombolytic agents such as tissue plasminogen activator and urokinase have been used, but there is no standard consensus in vasospasm and needs further study.[3] Kim and colleagues in their prospective study of cisternal irrigation for cerebral vasospasm, evaluated 40 subjects with 200 mg papaverine diluted in 500 ml ringer lactated solution irrigation continuously for 7 days, 39 subjects cisternal irrigation with 60,000 IU diluted in 500 ml ringer lactated solution irrigation continuously for 7 days and 42 subjects performing simple cisternal drainage, The results of this study show a significant decrease in vasospasm and lower incidence with intracisternal

administration of urokinase and papaverine compared with simple cisternal drainage.[17]

4. ENDOVASCULAR MANAGEMENT

The first treatment of vasospasm following SAH is pharmacological treatment including IV fluids, inotropic agents, vasopressors, and albumin.[2] In refractory vasospasm, which is not improved with pharmacological management or in special condition such as myocardial ischemia, pulmonary edema and congestive heart disease, endovascular treatment could be an alternative therapy.[2] Endovascular treatment for vasospasm includes mechanical dilatation with balloon angioplasty, and/or chemical dilatation using IA infusion or a combination of both.[2] Cerebral angioplasty with or without IA vasodilator is reasonable in symptomatic vasospasm, particularly in those which do not respond rapidly to hypertensive therapy (class IIa, level of evidence B).[7]

a. Balloon Angioplasty

Balloon angioplasty is widely performed in symptomatic vasospasm.[18] This technique was first introduced in 1984 by Zubkov et al.[2] The advantages of balloon angioplasty have been published and shown efficacy and safety to treat vasospasm in large cerebral vessels.[3] Improvement of CBF, neurologic condition, reduction velocities in TCD have been demonstrated in many publications.[3] The neurological improvement is about 90% and its better than natural history.[2] The best time to perform balloon angioplasty still remain debatable, but there is some indication that there is chance of better outcome if the patient is treated earlier and aggressively.[2] The study observed that the group in which endovascular management was performed within 2 hours after symptoms sustained clinical improvement compared with the group in which it was performed after 2 hours.[2]

Balloon angioplasty is limited to the proximal vessels (> 2-3 mm), usually at M1 and proximal M2 middle cerebral artery (MCA), segment A1 anterior cerebral artery (ACA), segment P1 posterior cerebral artery (PCA), basilar artery (BA), and supra clinoid internal carotid artery (ICA).[2] Anatomy of ACA is different to MCA. ACA is smaller than MCA with sharp angles to navigate especially when transverse to anterior communicating artery.[18] Balloon angioplasty at ACA is still challenging and not routinely done because of the safety and technical reasons.[18] Some factors that influence success of balloon angioplasty procedure at ACA are the size of distal vessel that accommodates the balloon, design of balloon, and the angulation of vessel.[18]

The limitation of this procedure is that distal balloon angioplasty is usually not feasible due to tortuosity of the vessel.[2] Balloon angioplasty is not free of risk, the major complication risk is about 5%.[2] Some of the complications include embolism, thrombosis, reperfusion injury, rupture of vessel, and displacement of surgical clips.[2] Fatal complication is perforation or rupture of vessel in about 1%.[2] The other complication is vasospasm recurrence after angioplasty.[2]

Chaudhry et al. in their study showed that this procedure is effective and safe and should be considered in vasospasm management.[18] They had evaluated efficacy of balloon angioplasty at ACA in vasospasm after SAH. The measurements of vasospasm are divided into 3 categories; severe vasospasm (> 50%), moderate vasospasm (25-50%) and mild vasospasm (< 25%). The changes in blood vessels after the procedure were measured. Results of this study found there was an increase in blood vessel caliber by about 94%, and 75% awake patients had neurological improvement and there were no intra-procedural complication such as vessel dissection and perforation, malfunction of device or thromboembolic phenomenon.[18] An RCT study has been performed, patients underwent prophylactic balloon angioplasty had significant reduction in the need for urgent rescue management for symptomatic vasospasm (12 vs. 26%, $p = 0.03$) but there was no statistical difference in cerebral infarction rate (23.5 vs. 31.8%, $p > 0.05$) or at 3 months outcome with relative risk reduction 29.4%, $p > 0.05$.[19]

Recently, there is no standard consensus about this procedure, but there is an agreement that widely used at M1 MCA, A1 ACA, P1 PCA, intradural internal carotid artery, intradural vertebral artery, BA are the targets vessels for balloon angioplasty.[3] Distal vasospastic vessels such as anterior communicating artery, posterior communicating artery, segment A2 and A3 ACA, M2 MCA, P2 posterior communicating artery can be treated with IA vasodilator and some case balloon angioplasty can be performed if indicated.[3]

Intra-Arterial Pharmacological Therapy

Mechanical and chemical angioplasty with vasodilator IA injection is widely used for vasospasm management and in some centers, is used as a first line management or prophylactically.[20] Mechanical angioplasty with balloon angioplasty is very effective for vasospasm but this procedure has limitation that smaller distal arteries are not compatible to this procedure.[20] IA pharmacological therapy is easier to perform and gives more benefit especially at distal part of cerebral arteries.[2] Selective infusion

of IA vasodilators to branches of small arteries is still beneficial although the effect is not long-lasting.[1] The potential disadvantages of this therapy are hypotension and increase of ICP related to vasodilatation and vascular relaxation.[2] Some medication that could be administrated IA include:[2]

a. **Papaverine**

Papaverine is group of benzylisoquinoline alkaloid, used IA for treatment of vasospasm since 1992.[2] The mechanism of action is vasodilator nonselective by inhibition contraction of smooth muscle of arteries and veins.[2] Papaverine inhibits cyclic guanosine monophosphate (cGMP), and cyclic adenosine monophosphate (cAMP) phosphodiesterase to elevate intracellular levels of cGMP and cAMP.[21] Papaverine also inhibit channels of calcium ions in membrane cell and blocks release of calcium from intracellular space.[21] The ideal timing to perform IA papaverine remains unclear, some literature suggests 2 hours after symptomatic vasospasm to restore CBF.[21] Multiple cases show that papaverine improves CBF, cerebral oxygenation, and circulation time.[2] Papaverine infusion IA successfully dilated one vascular territory, while 16% nimodipine infusion was ineffective, but there was no difference in capillary flow pre and post infusion.[22]

The dosage range varies from 3 to 5 mg/ml diluted in normal saline injected by micro catheter about 1 to 2 ml/min over 30 to 60 min, the total dosage is 100 to 600 mg per vessel infused over 20 until 35 min. The dosage and rate depends on ICP and mean arterial blood pressure.[3]

Some complications commonly happening are hypotension and increased ICP, so there is a need of ICP monitoring during infusion.[3] Other complications include neurologic decline caused by blood-brain barrier disruption, brain stem disorder with respiratory arrest, seizure, exacerbation of vasospasm paradoxically, gray matter area changes on MRI, and neurotoxicity manifested by neurologic deterioration.[3] Because of potential side effects, other agents are preferred compared with papaverine. But it is still used in some centers.[3]

b. **Nimodipine**

An experimental study reported that administration of IA nimodipine is more effective than administration of papaverine IA in vasospasm management.[2] Complications could occur such as hypotension, bradycardia, diarrhea, and rash.[2]

Bashir et al. evaluated clinical outcome and efficacy of IA nimodipine for vasospasm. A total of 25 patients enrolled to study, clinical condition measured by World Federation of Neurological Surgeons (WFNS) grade I-1V, and Fisher grade to detect subarachnoid blood, the efficacy of IA nimodipine assessed by clinical condition at 24 hours after it was administrated, and outcome measured by mRS score. This study showed a positive angiographic response in 95.1%, the clinical improvement occurred in 12%, and 20% had good outcome at three months follow up; 40% had moderate to poor outcome.[23]

A clinical study in intensive care unit found that 23% of the patients had improvement of neurological deficits and 83% had good clinical condition and this therapy can be considered as a low risk of treatment for refractory vasospasm.[24,25] Local IA nimodipine is also a high safety procedure and gives improvement in vasospasm; nevertheless there are some limitations such as there are no guidelines about selection of patients, duration of treatment or dosage of nimodipine.

c. **Verapamil**

The safety and efficacy of verapamil IA was reported in some cases.[1] Verapamil is a calcium channel blocker.[2] The mechanism is to decrease the calcium influx in smooth muscle cells which results in vasodilatation.[2] Verapamil IA has shown the increasing CBF as a linear function of cerebral artery pressure.[2] Verapamil could be used for management of mild vasospasm, moderate and severe vasospasm, and before performing balloon angioplasty procedure to prevent catheter-induced vasospasm in 2-3 mg verapamil IA.[2] There is no significant blood pressure or heart rate changes, also there is no increase of ICP.[2]

Lai et al. has shown that endovascular therapy could be an option in treating vasospasm caused by aSAH.[1] The study evaluated 7 aSAH grade 4 patients, and vasospasm was measured by CTA and/or TCD. The endovascular therapy underwent after 4-12 days and followed for at least 10 months. All patient received IA verapamil in dose of 8-40 mg depending upon the severity of vasospasm, site of injection, and vasospastic vessel position. A lower dose was considered in mild vasospasm. Some patients continued with percutaneous balloon angioplasty applied at ICA in 3 patients, ACA in 2 patients and MCA in 4 patients. There was no complication, about four patients had clinical improvement.[1]

d. **Nicardipine**

Intra-arterial (IA) nicardipine is commonly used in vasospasm therapy.[8] Nicardipine can significantly improve neurological condition and TCD velocities in cases of medically refractory patients.[3] Nicardipine

is metabolized in liver, the plasma level is influenced by liver function.[3] The plasma level is increased in patients with severe liver disease.[3] The half-life is about 40 min.[2] Some complication are prolonged hypotension, edema pulmonary, and renal failure.[8] Due to the complications and no improvement or poor outcome in many patients, it remains controversial.[8]

Nicardipine 0.15 mg/kg/h has improved angiographic vasospasm.[2] The other prospective, multicenter, randomized study using a low dose nicardipine IV 0.075 mg/kg/h showed lower incidence of angiographic and symptomatic vasospasm.[2] Basheli et al. evaluated the efficacy of vasodilator IA on outcome and MCA blood flow between day 1 until 15 when indicated clinically. A dose of 5 to 15 mg per vessel was considered based on angiographic effect, and hemodynamic condition. TCD was used to measure the vasospasm. This study showed efficacy of the IA vasodilator in preventing or reversing cerebral vasospasm after SAH, but no significant benefits in clinical outcome, so we still need some large cohort prospective studies to further evaluate.[26]

e. **Fasudil Hydrochloride**

Fasudil hydrochloride is a protein kinase inhibitor, potent vasodilator specific for cerebral arteries.[2,21] Mechanism of action is inhibition of rho-related kinase and rho kinase and blocking myosin light chain phosphatase.[3] Since 1995 fasudil has been widely used for vasospasm.[27] Fasudil inhibits inflammatory response by preventing monocyte and neutrophil infiltration.[27] Fasudil IA decreases cerebral circulation time after aSAH and is effective to avoid symptomatic vasospasm.[27]

IA fasudil hydrochloride 15 mg diluted in 20 ml normal saline injected about 15 min results in angiographic improvement, good outcome, and no significant changes in vital signs, such as blood pressure drop, response of symptomatic autonomic, and other side effects.[28] IA fasudil hydrochloride before symptomatic vasospasm can improve patient outcome and in patients with angiographic vasospasm can prevent vasospasm progression.[28] In a study to evaluate efficacy of fasudil hydrochloride IA for vasospasm, 51 angiographic vasospasm patients without any symptoms had improvement and 67% had immediate clinical improvement in angiographic vasospasm group with symptoms. There was no significant side effect from this procedure.[29]

f. **Milrinone**

Milrinone has a positive inotropic and direct vasodilatory activity.[2] It is cAMP specific phosphodiesterase selective inhibitor.[3] Vasodilatation is a result of elevated cAMP in vascular smooth muscle resulting in calcium uptake by sarcoplasmic reticulum, reduced calcium available for contraction and decreased vascular tone.[3] A retrospective analysis evaluated high dose of milrinone IA and milrinon-nimodipine IA in vasospasm patient. Standard 10-16 mg milrinone was administrated to the patients within 4 min, if there was refractory vasospasm, milrinone high dose 24 mg was given. If there was no increase in vessel diameter, nimodipine 5 mg was injected over 5-10 min. There was found an increase in the large vessel diameter following nimodipine plus milrinone injections.[20]

CONCLUSION

Vasospasm is a cause of morbidity and mortality after SAH. Several evidence based studies have shown that maintaining euvolemia and administration of nimodipine can prevent delayed cerebral ischemia. Some cases that do not show any response to first treatment should be considered for endovascular therapy such as mechanical angioplasty and administration of IA vasodilators to prevent further vascular injury. All management strategies are aimed at improving cerebral perfusion and reducing the inflammatory response due to vasospasm.

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