Impact Of Chemical Angioplasty

In patients with Vasospasm and Aneurysmal Subarachnoid Hemorrhage admitted under Neurosurgery department

Submitted for M.Ch Neurosurgery

By

Dr. GOWTHAM M

2019 - 2021

DEPARTMENT OF NEUROSURGERY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES& TECHNOLOGY

THIRUVANANTHAPURAM – 695011

Impact Of Chemical Angioplasty

In patients with Vasospasm and Aneurysmal Subarachnoid Hemorrhage admitted under Neurosurgery department

Submitted by: Dr. Gowtham M

Programme: M.Ch Neurosurgery

Month & year of submission: July- 2021

DECLARATION

This thesis titled ─ Impact Of Chemical Angioplasty In patients with Vasospasm and aneurysmal Subarachnoid Hemorrhage admitted under Neurosurgery department is a consolidated report based on a bonafide study of the period from August 2018 to July 2021, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of the MCh Neurosurgery examination.

Dr. Gowtham M,

Department of Neurosurgery,

SCTIMST, Thiruvananthapuram.

CERTIFICATE

CERTIFICATE

This is to certify that the thesis entitled — **Impact of chemical angioplasty in patients with Vasospasm and Aneurysmal Sub arachnoid Hemorrhage Admitted Under Neurosurgery Department** is a bonafide work of Dr. Gowtham M and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

Prof. Mathew Abraham, [guide]
Professor,
Department of Neurosurgery,
SCTIMST,
Thiruvananthapuram.

Dr. Mathew Abraham
M.S, M.Ch, F.R.C.S (Edin)
Professor of Neurosurgery
Sree Chitra Tirunal Institute for
Medical Sciences and Technology
Thiruvananthapuram
Reg. No. 23211 (T.C.M.C)

Dr. Jayadevan E R, [Co-guide]
Additional Professor,
Department of IR&IS,
SCTIMST,
Thiruvananthapuram.

CONSULTANT IN RADIOLOGY
SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011

Prof. Easwer H V,
Professor and H.O.D.,
Department of Neurosurgery,
SCTIMST,
Thiruvananthapuram.

Dr. EASWER H.V.
Professor & Head
Dept. of Neurosurgery
SCTIMST, Thiruvananthapuram

ACKNOWLEDGEMENT

I owe a deep sense of gratitude to Dr. Easwer H. V., professor and Head of the Department of Neurosurgery, for his invaluable advice, encouragement, and guidance, without which this work would not have been possible. His critical remarks, suggestions, helped me in achieving a high standard of work.

The guidance of Prof. Mathew Abraham, Professor, Department of Neurosurgery, has been invaluable and I am extremely grateful and indebted for his contributions and suggestions, which were of invaluable help during the entire work. He will always be a constant source of inspiration to me.

I owe a deep sense of gratitude to Dr. Jayadevan. E.R., Additional professor, department of IR&IS, Co-Guide, for his invaluable advice, encouragement, and guidance, without which this work would not have been possible. His critical remarks, suggestions, helped me in achieving a high standard of work.

I am deeply indebted to Dr. Krishnakumar K., Dr. George. c. Vilanilam, Dr. Jayanand Sudhir, Dr. Prakash Nair, Dr. Tobin George, Dr. Ganesh Divakar, and colleagues and I thank them for their constant encouragement and support.

I owe a deep sense of gratitude to all my patients without whom this work would not have been possible.

I am very grateful to my colleagues and teachers, Dr. Amjad, Dr. Jayapalsinh Gohil, Dr. Arvind, Dr. Harsha, Dr. Sanjay, and Dr. Sam for their constant encouragement and moral support.

Gowtham M

INDEX

Vasospasm and Aneurysmal Subarachnoid Hemorrhage

subarachnoid hemorrhage (SAH) remains a devastating neurological disease.[1] The common neurological complications post-SAH include rebleeding, hydrocephalus, and cerebral infarction associated with delayed cerebral ischemia (DCI) secondary to cerebral vasospasm. Efforts to prevent cerebral infarction are focused on improving brain perfusion.[2,3] Cerebral vasospasm is a delayed and self-limited condition that may occur when cerebral vasculature is exposed to the subarachnoid blood, usually after rupture of an aneurysm. Almost 70% of SAH patients will develop angiographic vasospasm; but, 40% of them will have clinical symptoms, and about 30% will develop delayed ischemic injury. Endovascular infusion of intra-arterial vasodilators and angioplasty are proposed as rescue procedures.[4] Among vasodilator agents, milrinone has emerged as a promising option. Milrinone is a selective phosphodiesterase 3 inhibitor that confers its positive inotropic and direct vasodilator properties. Milrinone has been successfully used to reverse cerebral vasospasm.[5]

AIM AND OBJECTIVES

Aim: This study aims to assess outcomes after chemical angioplasty in patients with subarachnoid hemorrhage with aneurysm rupture developing cerebral vasospasm

Objective: To assess the clinical and radiological impact of milrinone therapy in patients with sub arachnoid hemorrhage and aneurysms who develop cerebral vasospasm

REVIEW OF LITERATURE

Vasospasm

Cerebral vasospasm is a delayed and self-limited condition that may occur when cerebral vessels are exposed to the subarachnoid blood, usually after rupture of an aneurysm.

Angiographic vasospasm is evidence of arterial narrowing on vascular imaging.

Clinical vasospasm is narrowing of cerebral arteries causing cerebral ischemia with corresponding symptoms and signs [delayed ischemic neurological deficit]. Progression to cerebral ischemia depends mostly on the degree of arterial narrowing. and distribution among cerebral vasculature.

Vasospasm could be focal or diffuse involvement of vasculature. Based on the amount of narrowing, it can be mild, moderate, or severe in degree.

Historical aspects:

Around two centuries ago, an English physician Willaim Gull[6] , in 1859, had described an illness in which patient has suffered a fatal intracranial catastrophe, following which, up to 4th-day patient was verbalizing, but on the next day she died and the autopsy shows a thick clot in Sylvian fissure surrounding MCA and softening of the adjacent hemisphere, indicating stroke, and this description consistent with vasospasm. Later Florey [7]has directly observed spasm of vessels on mechanical and electrical stimulation in felines. Zucker[8], in 1944, observed substances in serum and platelets which can cause contraction of vascular smooth muscles and also described the vasoconstrictive activity of lysed red cells. In 1949,[9] Jackson described about a substance that invoked a good meningeal response was noted in red blood cells. Also in the same year, Robertson[6] has hypothesized that ischemic changes are due to temporary spasm of vessels rather than due to compression of vessels. In 1951, Ecker and Riemenschneider[10] described angiographic vasospasm of intracranial arteries and its relationship to the intracranial aneurysms. They said that spasm was greatest near the ruptured aneurysm and was most marked in the intracranial portion of the artery and it is a self-limited process and was not seen on angiograms done after 26 days after the hemorrhage. In the same year, Denny-Brown[11] considered hypotension as a causative

factor for disastrous outcomes in cerebrovascular accidents and advised raising the blood pressure to treat neurologic deficits. Later there have been attempts to reproduce this phenomenon in animals by injecting liquid blood, but they were unable to get the delayed ischemic phenomenon. In 1964, Stornelli and French [12]reported 28 patients with ruptured aneurysms and concluded that vasospasm is the pivotal factor determining recovery or death of patients. Allcock and Drake[13] published a large series of the ruptured aneurysm and opined that 'the shorter the time of angiography from the ictus event, more is the chance of vasospasm. But later studies have not confirmed this observation. Also, drake has stated that in ruptured aneurysms, vasospasm is the main cause of postoperative morbidity and mortality. In 1967, Kennady[14] considered the removal of blood in subarachnoid space by irrigation and also adding fibrinolysin. Next year, Simeone[15] has described a variety of physical and chemical factors that could cause angiographic vasospasm. Farhat and Schneider had described that elevation of blood pressure by 50-60mm Hg could result in prompt reversal of neurologic symptoms in acute cerebrovascular insufficiency. In 1970, Suzuki and associates[16] presented a mortality rate of 5% in 44 cases, concluded that patients could be operated early irrespective of angiographic vasospasm unless the patient was comatose or deteriorating. They also reported an incidence of 17% and noted that spasms have occurred most frequently between the second and fifth days after hemorrhage and were infrequently seen after 21 days. Suzuki and Yoshimoto,[17] in 1973, evaluated the prognostic indicators and found a patient's level of consciousness as the most reliable clinical parameter. They also recommended that surgery can be taken up within a week of subarachnoid hemorrhage if the patient's level of consciousness was not deteriorating. Wise[18] and colleagues were able to reverse neurologic deficits in some patients by employing vasopressors as a treatment for cerebral ischemia. Patients with focal ischemic symptoms were benefited with vasopressors even if they don't have hypotension. The clinical response was optimum with a 150-170mm. Hg range systolic and diastolic pressure to 85-100 mmHg. and most improvements were seen within an hour of administration of the therapy.

In 1974, Wernick[19] successfully treated post angiographic hemiplegia with vasopressor medications. Satio and [20]et al. found that vasospasm usually developed 4 days after the hemorrhage and subsided after 2 weeks of onset on an average. Osaka [21]presented evidence that prolonged vasospasm was produced by a breakdown of products of erythrocytes. Takemae[22] has substantiated the relationship between the amount of blood in cisterns and the development of vasospasm. On these observations,

they have advised early surgery to remove sub arachnoid clots. Sasaki et al.[23] proposed a theory of how oxy hemoglobin auto-oxidation and subsequent peroxidation of biomembrane can produce chronic vasospasm. Suzuki et al. later reported a high correlation between the presence of blood in subarachnoid cisterns in CT scan, episodes of loss of consciousness, and subsequent development of cerebral infarction. In 1980, Fischer[24] established the relationship between CT imaging findings and vasospasm. Later studies on cerebral blood flow demonstrated reduced cerebral blood flow, reduced metabolic rate, increased cerebral blood volume, and increase in oxygen extraction fraction. Takahashi[25] advocated the placement of cisternal drains to the removal of subarachnoid blood. Kassell presented data from large series of patients treated with induced hyertension and hypervolemia and shown reversal of neurological deterioration in approximately 80% of cases. Several complications like rebleeding of aneurysm, hyponatremia, and pulmonary edema were reported. George Allen in 1983, has come up with nimodipine, a calcium antagonist, treatment in cases of acute and chronic vasospasm and shown significant improvement with treatment.

Epidemiology:

An overall incidence of 50-90% of angiographic vasospasm was seen in aneurysmal SAH.[26]Moderate or severe vasospasm can develop in two-thirds of patients, half of these patients will develop symptoms, and a cerebral infarct will develop in approximately half of these symptomatic patients. A study analyzing 2741 patients, found that patients developed cerebral infarction at 26%incidence. The development of infarct was strongly associated with poor outcomes.[27] With new management strategies, the combined risk for mortality and morbidity due to vasospasm had reduced to less than 10%.[28]

Predisposing factors of Vasospasm-

A large and persistent clot in subarachnoid space is the most important risk factor for the development of vasospasm after aneurysmal SAH.[29] A study on subarachnoid clots on computed tomography also established a positive correlation between the amount of clots and the development of delayed cerebral ischemia[30]. This modified Fisher scale scores hemorrhage noted on CT brain imaging from 0 to 4.

Modified Fisher scale and risk for vasospasm

0-No SAH or IVH: carries very low risk for vasospasm

1-Focal or diffuse thin layer of SAH, no IVH: carries low risk for vasospasm

2-Focal or diffuse thin layer of SAH, IVH present: carries moderate risk for vasospasm

3-Focal or diffuse thick layer of SAH, no IVH: carries high risk for vasospasm

4-Focal or diffuse thick layer of SAH, IVH present: carries very high risk for vasospasm

Slow clot clearance from subarachnoid space has also been identified as an independent risk factor of vasospasm.[31] Poor neurological grade on admission, loss of consciousness at the time of rupture, cigarette smoking, diabetes mellitus, and pre-existing hypertension were the other potential predictors of vasospasm[32,33]. Distal anterior cerebral artery aneurysms had shown abnormally high incidence of vasospasm in a single- center study.[34] Some studies also proposed Japanese population and cocaine use could be independent predictors.[35]Spontaneous peri mesencephalic or prepontine SAH without evidence of aneurysm rupture was less prone for vasospasm.[36] Endovascular coiling, when compared to microsurgical clipping of aneurysms, claimed to be having a lower risk for the development of vasospasm[37] Intraoperative aneurysm rupture of the aneurysm was not seen to contribute to the development of vasospasm.[38]Impaired cerebral autoregulation, which could be assessed by transcranial Doppler, was predictive of vasospasm when detected during the first few days following SAH.[39]

Risk factors for vasospasm

-Thick subarachnoid clots

-Intraventricular hematoma

-Persistent subarachnoid clots (slow clearance)

-Poor neurological condition on admission

-Loss of consciousness associated with rupture

-History of cigarette smoking

-Pre-existing hypertension

-Diabetes mellitus

-Cocaine use

Pathogenesis:

Various theories have been proposed on the pathogenesis.

-Prolonged, mechanistically distinct biphasic vasoconstriction:

-Endothelin-1 overproduction (vasoconstrictor)

-Nitric oxide underproduction (vasodilator)

-Inflammation-mediated "remodeling" and narrowing of the arterial wall

-Combined processes

Smooth Muscle Contraction:

Vasospasm is caused by the contraction of vascular smooth muscle leading to prolonged arterial constriction. Hemoglobin will be released from subarachnoid blood clots and triggers the release of calcium and subsequently activates myosin light-chain kinase, induces cross-linkage of actin and myosin, and mechanical shortening of smooth muscle.

This process requires adenosine triphosphate along with calcium. Vascular smooth muscle depends on extracellular calcium stores.

During chronic vasospasm, contractile proteins like Rho kinase, protein kinase C, and tyrosine kinase have been implicated in vasospasm which will provide steady-state contraction in the absence of adequate intracellular calcium levels.[40] Sustained vasoconstriction is also associated with microscopic damage to the vessel wall layers. These microscopic changes include patchy necrosis in the media, ruptured internal elastic lamina, vacuolization, and loss of tight junctions of the endothelium .[41]

Endothelial Injury :

Methemoglobin and superoxide anion radicals are produced by the process of oxidation of the oxyhemoglobin present in the subarachnoid clots. Methemoglobin and superoxide anion radicals will act to cause lipid peroxidation.[42] Generated hydroxyl radicals and lipid peroxides permeate the vessel wall and injure endothelium and smooth muscle cells.[43] Damage to the endothelium is the key step in the pathogenesis of the establishment of vasospasm. Endothelial injury leads to defective endothelial nitric oxide (NO) production, a potent vasodilator, and overproduction of endothelin, a vasoconstrictor peptide.[44] The imbalance between NO and endothelin can cause vasospasm. Decreased availability of the NO contributes to the vasospasm; as

supported by the findings in several studies: (1) dysfunction of NO synthase in vasospasm, (2) NO scavenging by oxyhemoglobin, (3) NO donors reversing the vasospasm, (4) decreased cerebrospinal fluid nitrite levels.[45]Endothelin-1 (ET-1) is the predominant isoform of endothelin. It was found to have the greatest role in vasoconstriction. It is released from the tunica media and acts on surrounding vascular smooth muscle endothelin receptor A (ETA), to produce sustained vasoconstriction.[46] ET-1 values were seen to be elevated in patients with cerebral vasospasm. Inhibition of ET-1 production and antagonism of its effect has prevented vasospasm in animal models.[47]

So imbalance between the metabolism of NO and ET1 is thought to play a major role in pathogenesis.

Inflammation, Vessel Remodeling, and Vasospasm:

There is ampoule evidence that several inflammatory mechanisms are activated after SAH. There are hypotheses on these inflammatory processes being involved in the modification of the vessel wall extracellular matrix and smooth muscle cells. This mechanism is called "remodeling." Of vessel wall[48]. Several inflammatory cytokines, adhesion molecules, and extracellular matrix–regulating genes have been evaluated for the possible causation.[49,50] Elevated levels of plasma complement C3a is associated with poor outcome and increased intercellular adhesion molecule-1 have been linked to the development of vasospasm[51]Another study noted raised intrathecal levels of the cytokine interleukin-6 in patients prone for vasospasm.[52] Still the exact mechanisms underlying thr development of vasospasm are unclear.

Early brain Injury:

Early brain injury is caused by a sudden and acute elevation in intracranial pressure leading to global cerebral ischemia during the time of aneurysm rupture. This may initiate a series of pathological sequences which may play a role in pathogenesis, still under clinical trials. Several mechanisms including the breakdown of the integrity of the blood-brain barrier, cerebral edema, inflammation, cortical spreading depolarization, micro thrombosis have been thought to be involved in early brain injury. [53,54]

Clinical features:

Signs and symptoms of vasospasm usually result from ischemia in the region of the brain supplied by spastic vessels and raised intracranial pressure. Thorough and

vigilant bedside examination remains the most effective means of detecting early ischemia. Patients can have diminished attention, changes in verbal output, or a new pronator drift of the upper extremity, which are easy to be missed by beginners. Increased headache, either agitation or somnolence, change in patient behavior could indicate underlying vasospasm. If not detected, will lead to severe forms.[55]

Signs of vasospasm are usually referable to the vasospastic territory and are most easily identified. When a middle cerebral artery territory is involved patient will have upperlimb or lowerlimb weakness or involvement of both.When the dominant hemisphere is affected, associated aphasia will be evident.

Anterior cerebral artery vasospasm can be identified by leg weakness, as well as drowsiness, confusion, reduced speech output, and abulia.

Posterior territory vasospasm can cause more generalized neurological deterioration.

It is difficult to detect vasospasm in patients who have a poor neurological conditions. So, monitoring of comatose patients with auxiliary techniques should be done.

Early brain injury is due to an sudden elevation in intracranial pressure at the time of aneurysm rupture may initiate a series of pathological processes. They include cerebral inflammation, cortical spreading depolarization, micro thrombosis, blood-brain barrier breakdown, cerebral edema.[56,57]

Differential diagnosis:

- Increased cerebral edema
- Rebleeding of aneurysms or aneurysmal remnant
- Hydrocephalus
- Infection, including ventriculitis
- Hyponatremia
- Hypoxemia
- Cortical spreading depression
- Cerebral vasospasm causing cerebral ischemia

Many conditions can mimic vasospasm and should be ruled out simultaneously. Conditions like increased edema, rebleeding of the aneurysm, hydrocephalus, sepsis,meningitis, hyponatremia, hypoxia, and hypotension. They can precipitate or increase an underlying neurological deterioration.

DIAGNOSIS:

-Detectable neurological worsening, deficits referable to the ischemic territory

-Rule out all other differentials for delayed deficits

- Pathologic increases in TCD velocities; with velocities >200 cm/second ,high chance of large artery vasospasm

- Pathologic reductions in CBF can be detected by

Perfusion CT scanning

Single-photon emission computed tomography

Xenon-enhanced CT

Thermal diffusion flowmetry

-Detection of cerebral ischemia or infarction by

Diffusion-weighted magnetic resonance imaging

Near-infrared spectroscopy

Microdialysis

Direct probe cerebral oximetry

Jugular venous oxygen saturation

-Vascular imaging

Catheter-based angiography

CT angiography

Transcranial Doppler: [TCD]

Principle:As the diameter of a tubular conduit decreases, the flow velocity will increase within the conduit. In the same way, when an artery goes into spasm, the mean flow velocity increases within the artery. This increased velocity can be quantified by measuring the amount of doppler shift happened between the frequency of emitted and reflected ultrasound waves.

TCD is simple, non-invasive and can be done at the bedside. This makes it a frequently used technique to monitor SAH patients to look for any increase in mean blood flow velocity in intracranial vessels. TCD is effective in detecting proximal

vasospasm because of segmental and diffuse increases in blood flow velocity in these vessels when compared with more distally located vessels.[58] There is a good general correlation between TCD velocities and development vasospasm. TCD velocities in the MCA greater than 120 cm/second are indicative of some degree of vasospasm and velocities greater than 200 cm/second, are consistent with severe vasospasm.

Systemic blood pressure and overall cerebral blood flow can influence mean flow velocities in intracranial arteries. So, distinguishing vasospasm from these hyperdynamic conditions is necessary. So, to overcome this problem, Lindergaard ratio has been introduced.

A "Lindegaard ratio" of MCA mean flow velocity[VMCA] to the ipsilateral cervical ICA velocity [VICA]. VMCA/VICA greater than 3 denotes vasospasm. In hyperemia, mean flow velocity is increased both the vessels, so the ratio remains same.[59]

Similarly, a velocity ratio in the basilar artery to the extracranial vertebral artery is used to detect basilar artery vasospasm with more accuracy .[60]

Lindegaard Ratio	Angiographic Vasospasm
<3	No spasm
3–4.5	Mild spasm
4.5–6	Moderate spasm
>6	Severe spasm

58

Clinically, in patients with significant angiographic vasospasm , the Positive and negative predictive vlues of TCD when measured in MCA are close to 90%.[61] Additional maneuvers like transient, manual carotid compression can increase the sensitivity of TCD.[62] TCD is not reliable in detecting distal vasospasm.[63]

Cerebral blood flow and perfusion:

Single-photon emission CT,[64] quantitative stable xenon enhanced CT, and positron emission tomography[65] were used to evaluate defects in cerebral perfusion. But in the setting of critically inn patients performing these tests and repeating them will be a laborious task. Magnetic resonance imaging guided perfusion[66] and diffusion-weighted images[67] to look for ischemia has the same limitation. Perfusion CT scanning has been used for detection of ischemia in the setting of acute SAH[68]. Now it

is the most commonly used screening investigation modality to detect ischemia Also studies shown good correlation between CT angiogram and digital subtraction angiography.[69] It requires injection of bolus of contrast to calculate regional CBF. Cerebral ischemia can be detected based difference in perfusion on both sides or comparing CBF values and mean transit time.

Near-infrared spectroscopy (NIRS) is a useful tool for monitoring cerebral blood flow. It is simple, non-invasive and can be done on bedside.[70] NIR light has a wave length of 700-1000 nm. It penetrates skin,subcutaneous tissue and skull, and will get absorbed by oxy- and deoxyhemoglobin. Based on the amount of NIR light absorbed by hemoglobin, cerebral perfusion or oxygenation can be measured. NIRS will have two photodetectors with two light sources. NIRS allows for tissue sampling from a specific area and measure tissue oxygenation in that particular region. In one pilot study, NIRS was found to have more accuracy in detecting vasospasm compared to TCD.[71]

MICRODIALYSIS It is measurement of extracellular concentrations of glutamate, lactate, pyruvate, glucose, and glycerol in brain tissue by means of cerebral microdialysis catheters. Elevated lactate levels can be used as a screening tool as a surrogate marker of excititoxic cell injury. Glutamate and lactate are the most important markers. Glutamate and lactate values increase 24 hours before clinical ischemia sets in . Elevaed lactate/pyruvate ratios and lactate/glutamate ratios were good prognostic indicators in SAH.[72]

VASCULAR IMAGING:

Digital subtraction angiography or computed tomographic angiography are the two important imaging techniques which cn visualize vasospastic vessels.[73] Magnetic resonance imaging is difficult to carry out in critically ill patients.[74]

Sensitivity of Computed tomographic angiography is 80% and specificity is of 93%. But, clip artifacts render CT angiogram inferior to digital angiogram in providing adequate detail. It is only used as an initial screening tool to rule out vasospasm.[75]

Catheter-based angiography or digital subtraction angiography is the best method of diagnosing vasospasm.

Angiographic vasospasm is narrowing of the vessels which could be focal, segmental, or diffuse. Angiographically vasospasm is graded as mild (<25%), moderate (25% to 50%), or severe (>50%) degrees. The spasm will be established after comparing it with the baseline imaging.

Circulation time: It is measured as the time interval from the maximum filling of the carotid siphon to the maximum filling of parietal veins. The normal circulation time is 3.43+/- 0.51 sec.[76] Cerebral circulation time is an indirect measure of cerebral blood flow, so any improvement in circulation time will correlate with the increase in cerebral blood flow.[77]

Prevention Of Vasospasm:

General measures

-Maintain euvolemia

-Prevent anemia (hemoglobin <9 g/dl)

-Prevent hyponatremia

-Maintain normal to high systemic blood pressure

-Optimize ventilation and oxygenation

-Prevent high ICP (and maintain CPP) with external ventricular drainage as necessary

-Nimodipine, 60 mg by mouth or nasogastric tube every 4 hours

Augmentation of subarachnoid clot clearance

-Clot lysis

-Lamina terminalis fenestration

-Lumbar CSF drainage

-Combined management

Patients have a high chance of developing hypovolemia in the setting of acute SAH[78] and this hypovolemia should be avoided. So initially patients were managed with hypervolemia in an attempt to prevent vasospasm, but it was unproven. There were no proven results that induced hypervolemia was beneficial in preventing vasospasm or ischemia.[79,80] . Patients were hydrated well, and there were some studies had shown additional colloid infusions were beneficial. [81] SAH patients have an increase in brain natriuretic peptide, which will increase sodium loss and can lead to hyponatremia, a condition known as “cerebral salt wasting syndrome”. Hyponatremia could increase the risk for vasospasm [82]. Cerebral salt wasting and hyponatremia should be managed with salt replacement with the infusion of normal saline or 3% hypertonic saline, and if required, fludrocortisone should be given. [83]

Blood transfusion and anemia are other factors that could contribute to morbidity

related to vasospasm[84]. Hemoglobin should be maintained at or more than 9 gm% to maintain adequate cerebral oxygen delivery. The other component of triple 'H' therapy is hypertension. Hypertension is maintained after the clipping of an aneurysm to prevent vasospasm. Adequate oxygenation, normothermia, prevent hyperglycemia, monitoring sodium, calcium, and magnesium should be done to prevent vasospasm.
Nimodipine can be administered orally or via a nasogastric tube at a dose of 60 mg every 4 hourly. It is continued for 3 weeks in patients with aneurysmal SAH.[85]

Prophylactic balloon angioplasty was tried, which doesn't show any added advantage and the safety was questionable.[86] Intracisternal thrombolysis with recombinant tissue plasminogen activator and in some studies tried used urokinase was tried. They have shown that these agents help in faster clearance of subarachnoid hemorrhage, leading to less incidence of vasospasm and less cerebral ischemia.[87] Lamina terminalis fenestration at the time of clipping of aneurysm had shown to reduce the incidence of vasospasm and hydrocephalus. Increased cerebrospinal fluid flow and faster clearance of clots from subarachnoid space are brought by this fenestration.[88] In a single-center cohort study, Intra thecal vasodilators like prolonged-release nicardipine impregnates were placed in the subarachnoid space in patients with thick SA.[89] Similarly, papaverine pellets were also tried.[90] Both studies have shown good outcomes in terms of the prevention of vasospasm. These results led to a phase II randomized trial with nicardipine pellets and shown favorable results.[91] IMASH and IMASH 2 trials have used intravenous magnesium, which has shown that magnesium did not affect vasospasm or clinical outcome.[92] The ETA/B receptor antagonist was found to have decrease delayed ischemia but had no apparent effect on the outcome.[93] Also, clazosentan, the ET_A receptor antagonist, had initially shown favorable outcomes in phase IIa studies, but, failed to show this positive effect in human trials. Statins were also tried in the management of vasospasm. Because of their hypolipidemic activity and effectiveness in improving endothelial function, and reducing inflammatory responses, they were thought to reduce the effects of vasospasm. But meta-analysis showed that addition of statins had not provided any additional benefits.[94,95]

Reversal Vasospasm

Triple-H Therapy: It consists of Hypervolemia, Hypertension, and Hemodilution

Triple H therapy is thought to increase cardiac output and then increase cerebral perfusion pressure. Along with this change in blood rheology helps in improving

oxygen transport.

Induced hypertension was found to be more effective than aggressive hypervolemia. Also, hypervolemia has many associated complications.[96] In patients with secured aneurysms, vasospasm should be treated with induced hypertension ideally with phenylephrine or norepinephrine.[97] The key concept is a rapid increase in blood pressure, regardless of the agent used. The complications associated with triple 'H' therapy are cardiac failure, pulmonary edema, pneumothorax, cerebral edema, and increased intracranial pressure. Elderly patients and patients with the pre-existing cardiopulmonary disease are at an increased risk of these complications.

Even though this was widely used, 'triple-H' had not yet been demonstrated to affect outcomes to a significant levels for cerebral vasospasm. Moreover, there is no good evidence from randomized controlled studies. Egge et al.[98] have randomized patients with and without receiving triple H therapy and there were no differences in the incidence of clinical or transcranial Doppler vasospasm, cerebral blood flow measurements, or long-term outcomes (Glasgow Outcome Scale score at 1 year) between the two groups. More recent data also suggest that induced hypervolemia is an ineffective approach and maybe detrimental[91,99,100]. Also hemodilution, blood transfusion had been associated with increased rates of angiographic vasospasm, cerebral ischemia, and worse functional outcomes in SAH patients [101]. But, patients undergoing normovolemic-induced hypertension were the only ones to show a significant increase in brain tissue oxygenation[102]. These data suggest that moderate hypertension with a cerebral perfusion pressure of 80–120 mm Hg, in a normovolemic patient is an effective method when compared to hypervolemic hypertensive therapy. Normovolemic hypertensive therapy had lesser complications and resulted in better cerebral oxygenation.

Endovascular Therapy

The most common modalities used in the endovascular

treatment of cerebral vasospasm is pharmacological dilatation with intra-arterial (IA) drug infusion, mechanical dilatation with balloon angioplasty, or a combination of both.

Intra arterial pharmacological therapy:

Pharmacological dilatation with IA drug infusion has the advantages of more distal penetration in the cerebral arterial system and a better safety profile. In addition, it is easier to perform, and in many cases, drug administration can be performed through a

diagnostic catheter positioned in the internal carotid or vertebral arteries. Elevations in ICP was an important drawback of IA drug infusion. Recurrent vasospasm requiring multiple treatments or infusions is also an another important disadvantage.

Many drugs have been tried for reversal of vasospasm Intra arterially. Papaverine, Nicardipine, verapamil, Nimodipine, Fasudil hydrochloride, Colforsin Daropate Hydrochloride, Amrinone, Milrinone have been tried, which have shown promising results in relieving spasm.

Papaverine:

Papaverine is a benzyl isoquinoline alkaloid derived from opium. It is a potent nonselective vasodilator and its mechanism of action is due to result from inhibition of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate phosphodiesterases in the smooth muscle, and inhibition of calcium ion channels in the cell membrane, resulting in vasodilation by inhibition of smooth muscle contraction[103,104].

Multiple studies demonstrated angiographic reversal with papaverine infusion. Kaku et al. [97] performed super selective IA infusion of 0.2% papaverine hydrochloride in 37 vascular territories of 10 patients with symptomatic vasospasm. 8/10 patients showed improvement in neurological function after the procedure. There were no serious side effects. Conversely, transient focal neurological deficits were seen in 44% of the patients who received a high-concentration (0.8–2%) IA papaverine infusion in another study[105]. Increase in ICP was a known complication after IA infusion of papaverine demonstrated in many studies[106]. This sustained ICP could be correlated with poor outcomes in these patients. This side effect is likely related to an increase in CBF and venous capacitance from diffuse vasodilatation. Now papaverine is not used for intraarterial infusions

Nimodipine:

Nimodipine is a dihydropyridine compound, a calcium channel antagonist that blocks the influx of extracellular calcium into L-type voltage-gated calcium channels. Nimodipine appears to reduce smooth muscle contraction and decrease the release of vasoactive substances from the endothelium and platelets. It does not reduce angiographically detectable vasospasm. It also has a neuroprotective effect. Its neuroprotective effects are thought to be due to the prevention of calcium overload in ischemic neurons [107,108]. Nimodipine complications include hypotension, bradycardia,

diarrhea, and rash. Rare cases of refractory hypotension have been reported [109].

Both oral and intravenous nimodipine can be used. Nimodipine has been shown to decrease the incidence of cerebral infarction and improve outcomes after aneurysmal and traumatic SAH [110,111].

Biondi et al.[101] studied the efficacy of IA nimodipine in preventing infarcts in 25 consecutive patients with symptomatic vasospasm.

Nimodipine was infused intra-arterially through a diagnostic catheter at a rate of 0.1 mg/min. Postprocedural clinical improvement and favorable outcomes were seen in 76 and 72% of the patients, respectively. But among these patients, significant vessel dilatation was seen in only 43% of the patients. So there nimodipine has an additional possible underlying effect on neuroprotection and microcirculation.

For vasospasm prevention Oral Nimodipine is given for 21 days and typically dosed as 60 mg every 4 hours for SBP 140 mm Hg, 30 mg every 4 hours for SBP 120 to 140 mm Hg, and held for an SBP below 120 mm Hg.

Milrinone

Milrinone is a bipyridine methyl carbonitrile analog to amrinone. Its direct vasodilatory activity on vascular smooth muscle cells and positive inotropic properties were used in reversing the vasospasm. It selectively inhibits cAMP-specific phosphodiesterase III isoenzyme in the cardiac and vascular muscle. Vasodilatation occurs due to an increase in cAMP levels in the smooth muscle, facilitating more calcium entry into the sarcoplasmic reticulum, reducing the amount of calcium available for actin-myosin coupling and thereby reducing vascular tone[112]. Milrinone has a half-life of approximately 50 min. Initially, it has been used effectively for the prevention of cerebral vasospasm in a canine model[113].

Arakawa et al. [114]first studied milrinone effects in seven patients with symptomatic vasospasm . These patients were given both intraarterial and intravenous milrinone. Initially IA route and subsequently intravenous administration of milrinone was done. Milrinone of 0.25 mg/ml concentration was given intra-arterially at a rate of 1 ml/min. Maximal total dose was from 5 to 15 mg.

An intravenous infusion was then started at 0.5 or 0.75 μg/ kg/min dose.This intravenous infusion was continued upto 14 days from the day of SAH.

This study shown an adequate dilatation in all patients, and with 78% mean increase in vessel diameter. CBF was increased on both hemispheres.

Only three among seven had recurrent vasospasm and two of them required mechanical angioplasty. There were no significant cardiovascular effects. 60% patients had good neurological outcome, which was significant improvement compared to previous studies with other agents. Fraticelli et al. [115]studied similar cobined IA and Intravenous administration of milrinone. The results showed a significant increase in diameter of vasospastic vessels and a moderate increase in heart rate with no significant change in arterial pressure. Later milrinone was administered in route of cisternal irrigation which shown positive results in prevention of vasospasm[116].

So, Milrinone has been used widely to reverse vasospasm. Studies also shown combined administration of nimodipine and milrinone is tolerated well and synergistic effect was seen in prevention and treatment of vasospsasm.

MATERIALS AND METHODOLOGY

Study group: Patients admitted under the Department of Neurosurgery, SCTIMST, Trivandrum, from the years August 2018 to January 2021, with aneurysmal subarachnoid hemorrhage, operated and who developed vasospasm in the post-operative period are studied. we performed a prospective retrospective study to assess the difference in the outcome of vasospasm secondary to aneurysmal subarachnoid hemorrhage who are treated with digital subtraction angiography and chemical angioplasty. This prospective retrospective observational study was started after getting IEC clearance.

A total of 20 consecutive patients were included in this study, who met the inclusion criteria. 14 patients were admitted between August 2018 to December 2019. These patient's details were collected retrospectively from institute electronic medical records. The rest of the six patients were admitted between January 2020 to January 2021. These six patients' hospital course was followed prospectively. All patients underwent transcranial clipping of aneurysm, after which they will be monitored in the neurosurgery intensive care unit. All patients upon suspected vasospasm have undergone digital subtraction angiography and chemical angioplasty with milrinone upon confirmation. Results were compared in the form of clinical and radiological outcomes, morbidity as well as mortality. All patients were followed up at 2 weeks following surgery, 6weeks, and 3 months. Four patients who did not respond to chemical angioplasty also received balloon angioplasty therapy.

Inclusion criteria :

- All patients with Aneurysmal subarachnoid hemorrhage with vasospasm undergoing chemical angioplasty will be participants of this study.

- Both sexes.

Exclusion criteria :

- patients with SAH secondary to AVM/ trauma
- Patients who underwent coiling of the aneurysm.

Funding: No funding used.

Workup plan: All patients Patient presenting with SAH on Computed tomograph and aneurysm on angiogram, will be admitted under the Department of Neurosurgery. Patient clinical condition assessed by Glasgow coma scale and CT severity of sub arachnoid hemorrhage will be assessed by WFNS grading and modified Fischer grading. Preoperative investigations will include routine blood and urine workups, in addition to radiological assessments. All patients will be started on T. Nimodopine 60mg., Q4- hourly. The patient will undergo clipping of the aneurysm. All patients will be monitored in the neurosurgery ICU. Continuous nimodipine infusion will be given intravenously till oral/ ryles tube feeds are started. Patients will be monitored for vitals and repeated neurologic examinations every hourly, for detection of any deterioration. Patients with a change in sensorium, the neurological status will be suspected to have Vasospasm and will be taken up for DSA for confirmation. Simultaneously, Patients will be investigated for hyponatremia, hypoxia, seizure and postictal state, or new-onset infarct. On confirmation of vasospasm, patients will be treated with milrinone intraarterially, which will be infused at a rate of 8 mg over 30 minutes in the main artery dedicated to the territory of the artery in vasospasm i.e. internal carotid artery or dominant vertebral artery. The infusion will be repeated once in the same territory if there is an incomplete reversal. Milrinone infusion can be repeated in a other territory in a situation of extensive vasospasm, with a maximum dose of 24 mg. Radiologists performing DSA will assess the efficacy of intraarterial infusion by measuring angiographic enlargement of the vessel diameter and circulation time. Later all patients will be assessed in NSICU, every half an hour, for conscious level [Glasgow Coma Scale - GCS], improvement in deficits if any, and changes in CT brain. All patients will receive a continuous intravenous infusion of milrinone. If patient tolerates the infused dose, the dose was gradually increased from

0.5 mcg/kg/min to 1.5 mcg/kg/min to maintain relatively high plasma concentrations of the drug after intraarterial infusion. This dose incrementation will be stopped if the patient develops tachycardia (HR >100 bpm) or >20% drop in blood pressure. Later according to the response to the treatment, the patient will be taken up for check angiography to look for recurrent vasospasm and treated with chemical angioplasty. If the patient develops spasm for a third time or spasm refractory to chemical angioplasty, will be taken up for balloon angioplasty. Patients will be assessed for change in sensorium[GCS], improvement in deficits if any, and changes in CT brain. Patient response to angioplasty will be assessed by the means of Glasgow coma scale [GCS]and modified Rankin score, clinically, at the time of discharge. Also modified Rankin score will be assessed at 6weeks follow-up and 3 months follow-up.

Glasgow Coma Scale

Eye Opening Response

•4- Spontaneous--open with blinking at baseline

•3- To verbal stimuli, command, speech

•2-To pain only (not applied to face)

•1- No response

Verbal Response

•5- Oriented

• 4-Confused conversation, but able to answer questions

• 3-Inappropriate words

• 2-Incomprehensible speech

• 1-No response

Motor Response

• 6-Obeys commands for movement

• 5-Purposeful movement to painful stimulus

• 4-Withdraws in response to pain

• 3-Flexion in response to pain (decorticate posturing)

• 2-Extension response in response to pain (decerebrate posturing)

• 1-No response

Head Injury Classification:

Severe Head Injury----GCS score of 8 or less

Moderate Head Injury----GCS score of 9 to 12

Mild Head Injury----GCS score of 13 to 15

The **WFNS scale** is as follows:

Grade 1 – Glasgow Coma Score (GCS) of 15, motor deficit absent

Grade 2 – GCS of 13-14, motor deficit absent

Grade 3 – GCS of 13-14, motor deficit present

Grade 4 – GCS of 7-12, motor deficit absent or present

Grade 5 – GCS of 3-6, motor deficit absent or present

Modified Fisher scale and risk for vasospasm

0-No SAH or IVH: very low risk

1-Focal or diffuse thin layer of SAH, no IVH: low risk

2-Focal or diffuse thin layer of SAH, IVH present: moderate risk

3-Focal or diffuse thick layer of SAH, no IVH: high risk

4-Focal or diffuse thick layer of SAH, IVH present: very high risk

Modified Rankin Score

Score and Description

0 - No symptoms at all

1 - No significant disability despite symptoms; able to carry out all usual duties and activities

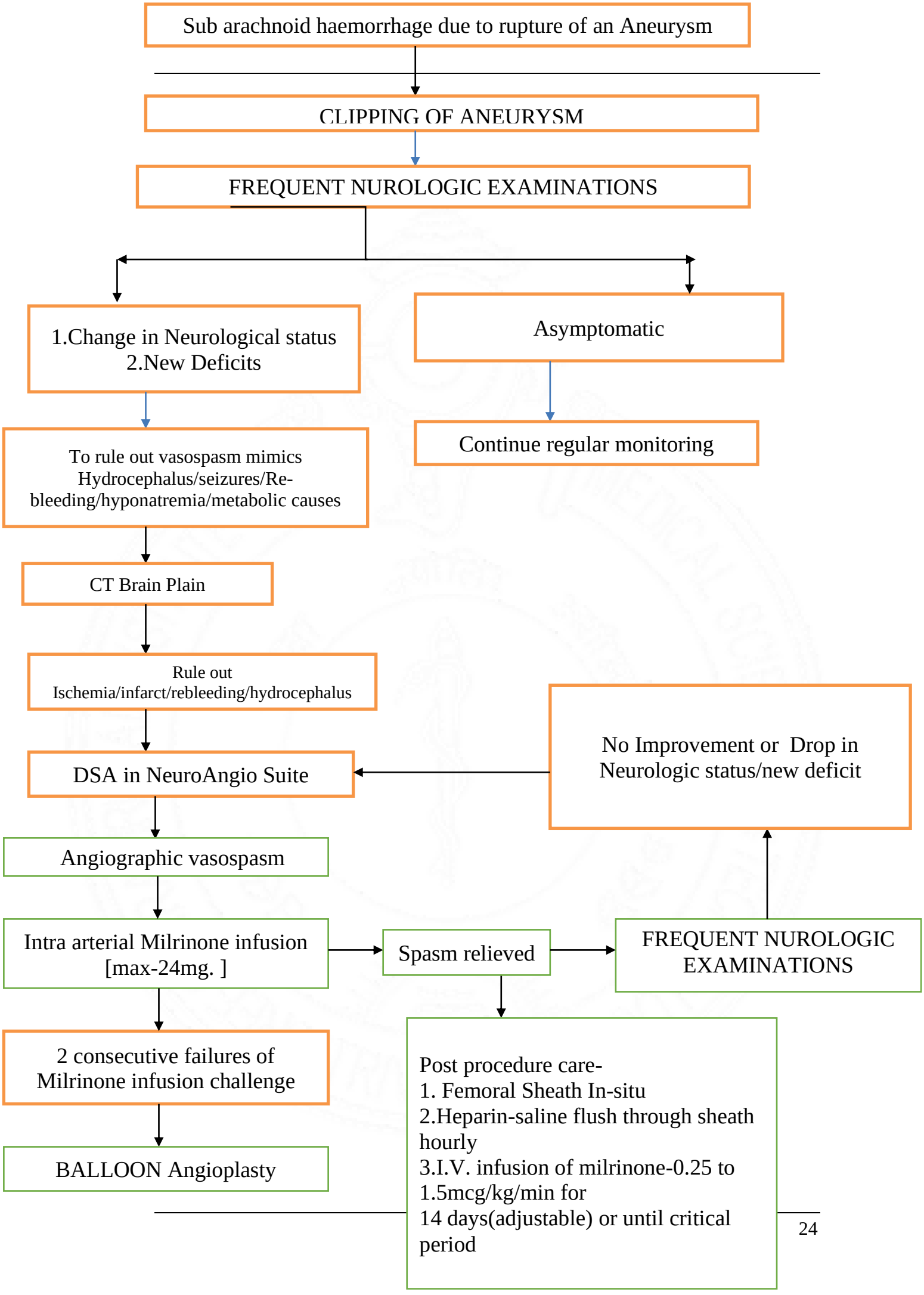
2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 - Moderate disability; requiring some help, but able to walk without assistance

4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 - Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

6 - Dead


Sub arachnoid haemorrhage due to rupture of an Aneurysm
CLIPPING OF ANEURYSM
FREQUENT NUROLOGIC EXAMINATIONS
1.Change in Neurological status
2.New Deficits
Asymptomatic
Continue regular monitoring
To rule out vasospasm mimics
Hydrocephalus/seizures/Re-bleeding/hyponatremia/metabolic causes
CT Brain Plain
Rule out
Ischemia/infarct/rebleeding/hydrocephalus
DSA in NeuroAngio Suite
No Improvement or Drop in Neurologic status/new deficit
Angiographic vasospasm
Intra arterial Milrinone infusion [max-24mg.]
Spasm relieved
FREQUENT NUROLOGIC EXAMINATIONS
2 consecutive failures of Milrinone infusion challenge
BALLOON Angioplasty
Post procedure care-
1. Femoral Sheath In-situ
2.Heparin-saline flush through sheath hourly
3.I.V. infusion of milrinone-0.25 to 1.5mcg/kg/min for
14 days(adjustable) or until critical period

RESULTS and ANALYSIS

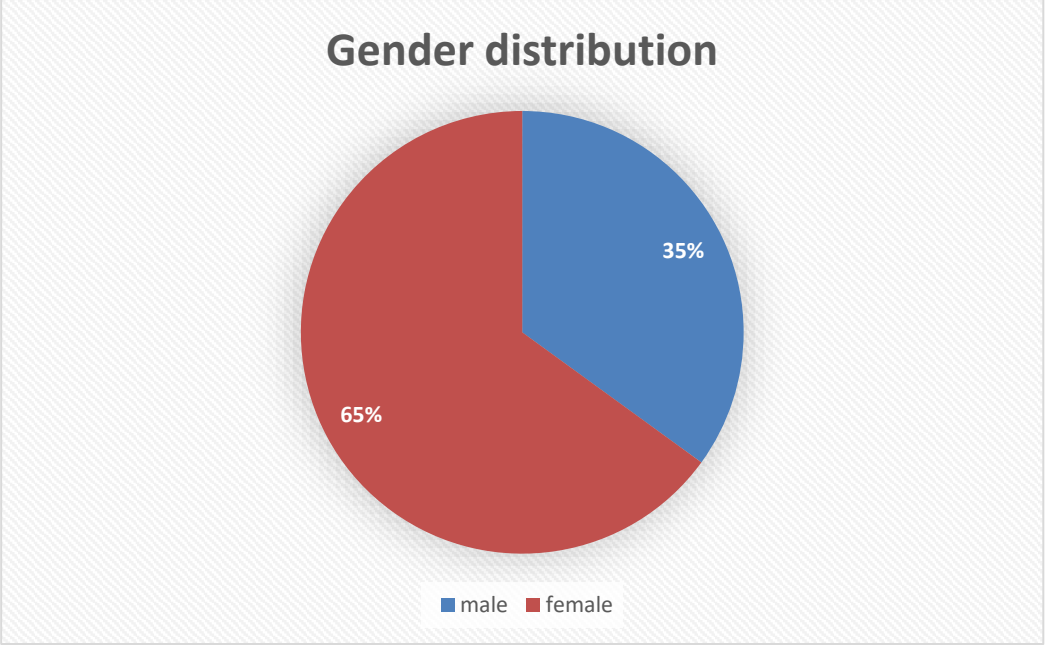
Our study comprises the clinical and radiological outcomes of 20 consecutive patients who underwent chemical angioplasty with milrinone intraarterially.

PATIENT DEMOGRAPHICS

- **AGE and SEX Distribution:** A total of 20 consecutive patients were included in the study for 2.5 years i.e. from august 2018 to January 2021. Out of these, 7 cases were male, and 13 cases were female, with a female: male ratio of 1.8: 1. The minimum age was 47 years and the maximum age was 70 years. The mean age was 57.55 years.

Table 1 Gender Distribution

Gender	Number Of Patients	Percentage Of Patients
Male	07	35%
Female	13	65%
Total	20	100%



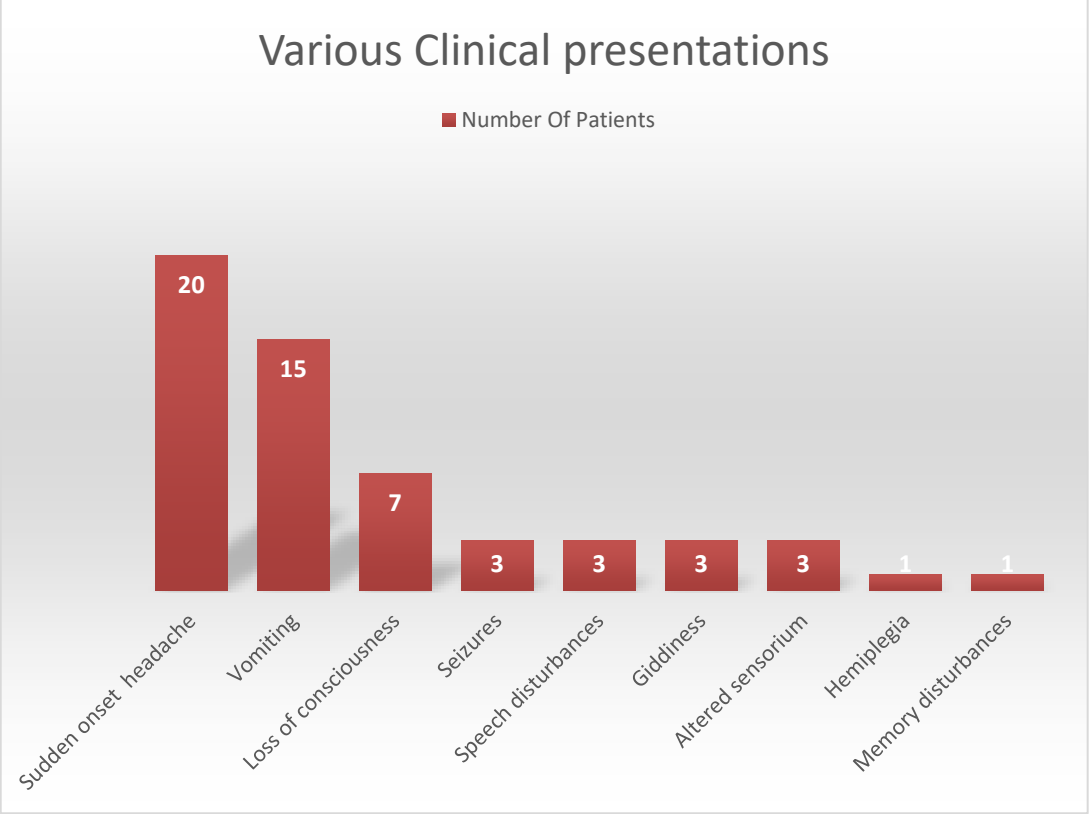
Clinical Presentation:

Sudden onset severe headache was the most common presentation among all the patients. Vomiting was the next common presenting symptom. Other presentations being the loss of consciousness, seizures, speech disturbances in form of either slurring or aphasia, giddiness, altered sensorium, hemiplegia, and memory disturbances in that order of frequency and the number of patients presented with particular symptoms being shown in below tabular form and graphic representation.

Table.2. Patient Clinical presentation

SYMPTOM	Number Of Patients
Sudden onset severe headache	**20**
Vomiting	**15**
Loss of consciousness	**7**

Seizures	**3**
Speech disturbances	**3**
Giddiness	**3**
Altered sensorium	**3**
Hemiplegia	**1**
Memory disturbances	**1**

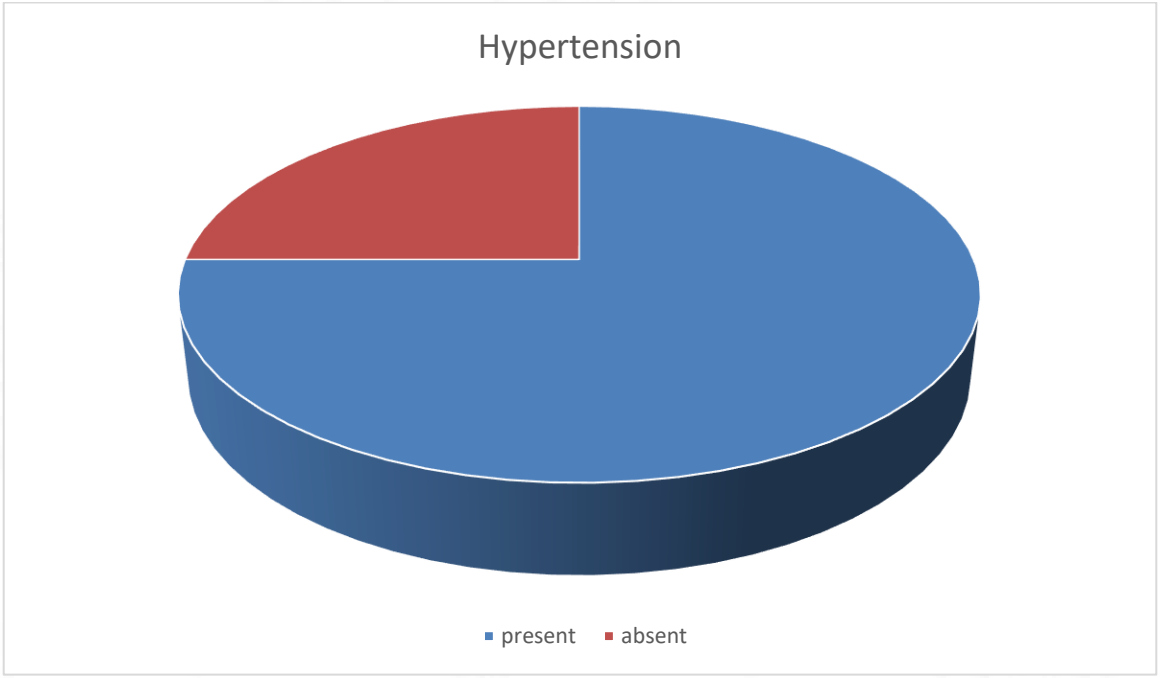


Distribution according to the presence of Hypertension:

Among the 20 patients, 15 were hypertensives, constituting 75% of the study population.

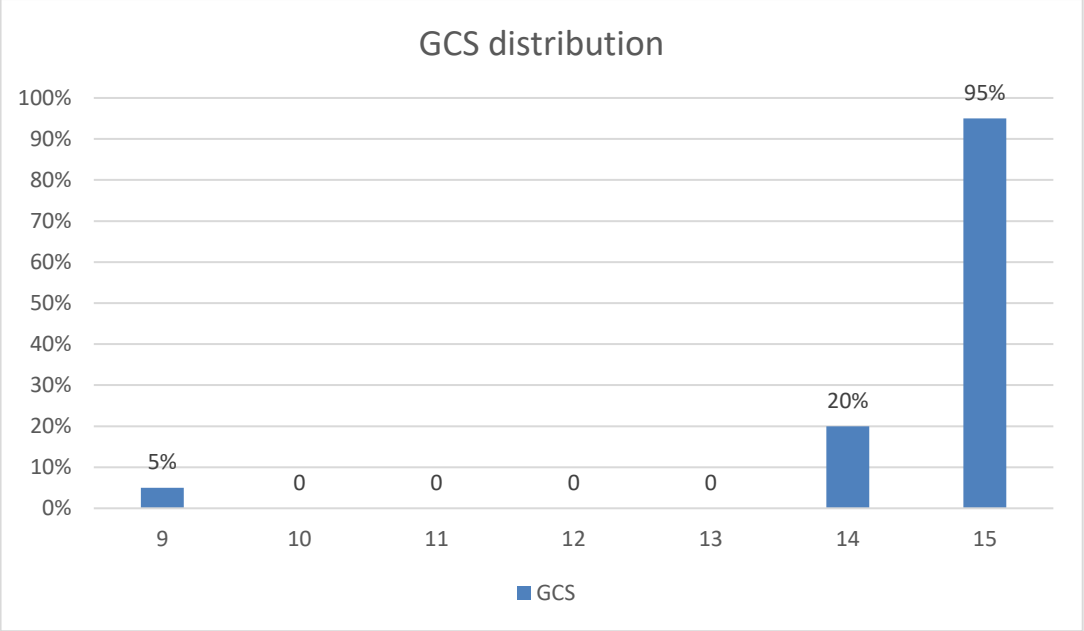
Table 3: Hypertension among the study group.

Hypertension	Number of patients	Percentage
Present	15	75%
Absent	05	25%
Total	20	100%



GCS at the time of presentation :

15 patients had GCS of 15, constituting 75%, 4 individuals had GCS of 14 and one (5%) had a GCS of 9.



Smoking History:

Four patients [20%] had a history of cigarette smoking.

Distribution of Location of aneurysms :

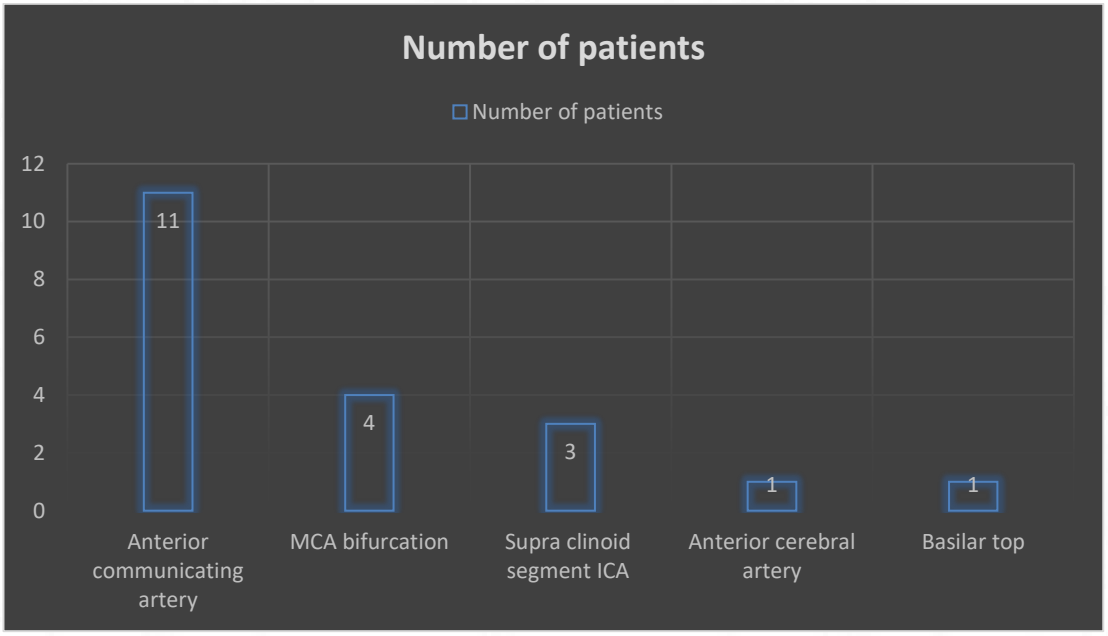
Anterior circulation aneurysms constituted 95% of the study population, whereas one patient had a basilar top aneurysm and two patients had more than one aneurysm.

Among the anterior circulation aneurysms, eleven patients had anterior communicating artery aneurysms, four patients had middle cerebral artery [MCA] bifurcation aneurysm, three aneurysms located in supra-clinoidal segment ICA, one patient had anterior cerebral artery [A3 segment] aneurysm.

Table 4: Distribution of Location of aneurysm

Location of aneurysm	Number of patients	Percentage [%]
Anterior communicating artery	11	55

MCA bifurcation	04	20
Supra clinoid segment ICA	03	15
Anterior cerebral artery	01	5
Basilar top aneurysm	01	5

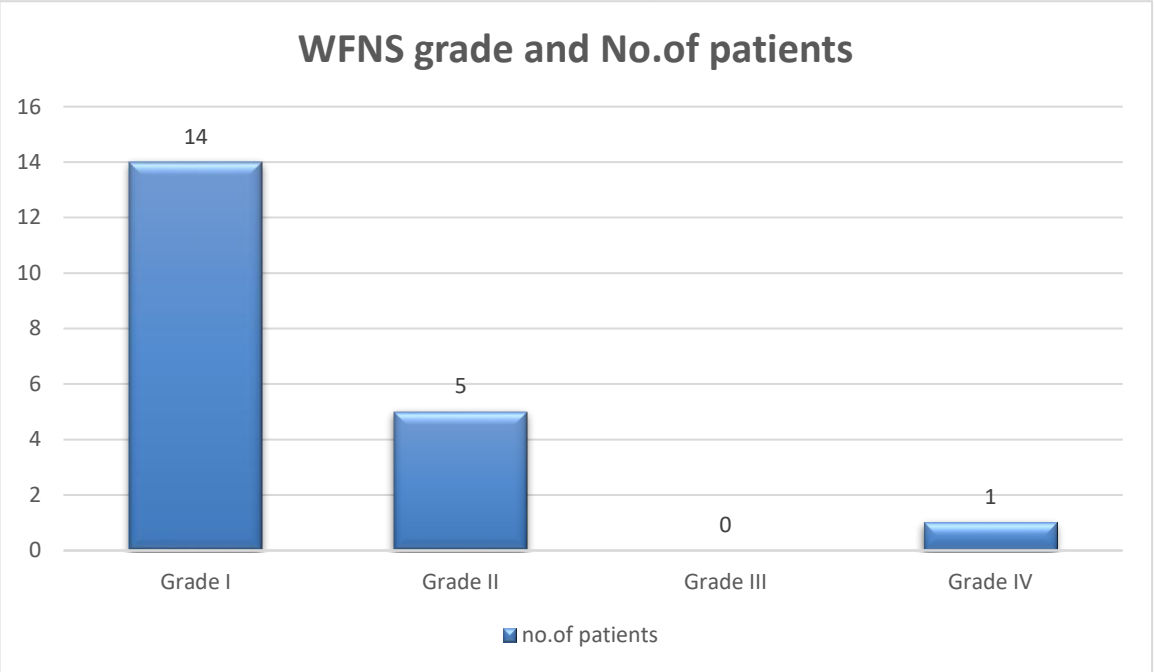


Distribution according to the WFNS grading:

Table 5 shows the WFNS grade distribution among the study group

WFNS Grade	Number of patients	Percentage (%)
I	14	70

II	05	25
III	00	0
IV	01	5

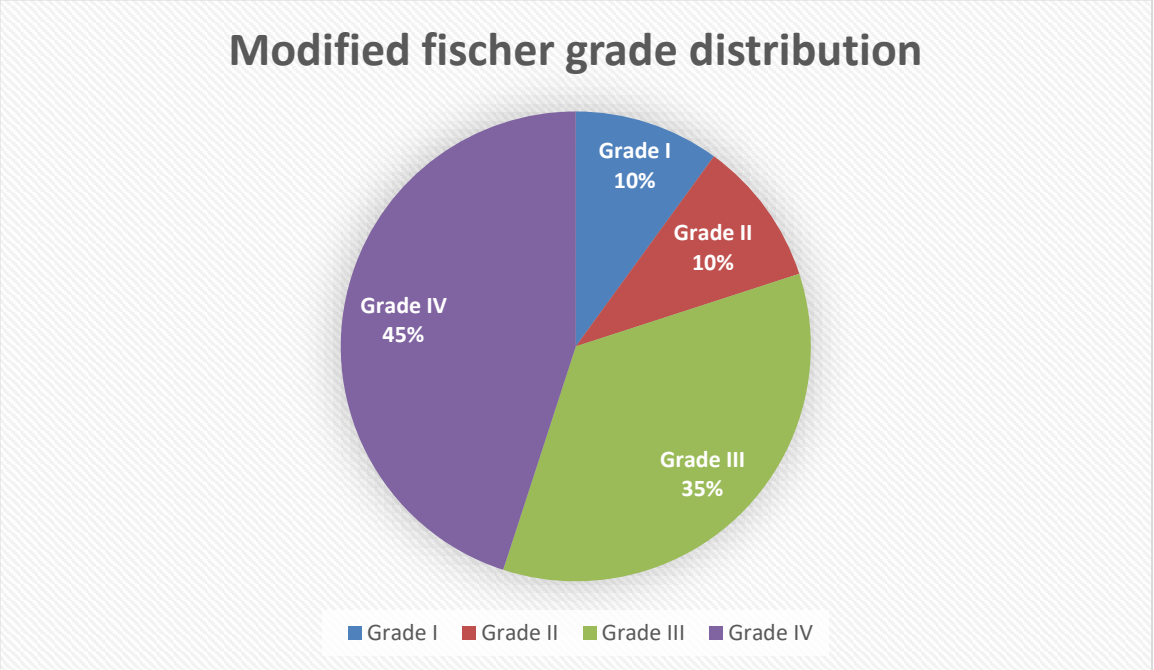


Distribution according to the Modified Fischer grading:

Table 6 shows the Modified Fischer Grade distribution among the study group

The Modified Fischer Grade	Number of patients	Percentage (%)
I	02	10
II	02	10

III	07	35
IV	09	45



Operative details :

- **Timing of the surgery:**
- The majority number of patients underwent surgery within the first week of the date of bleed [SAH]. Patients were operated on between 3 to 16 days from the date of bleed, averaging 6.8 days from the date of bleed.

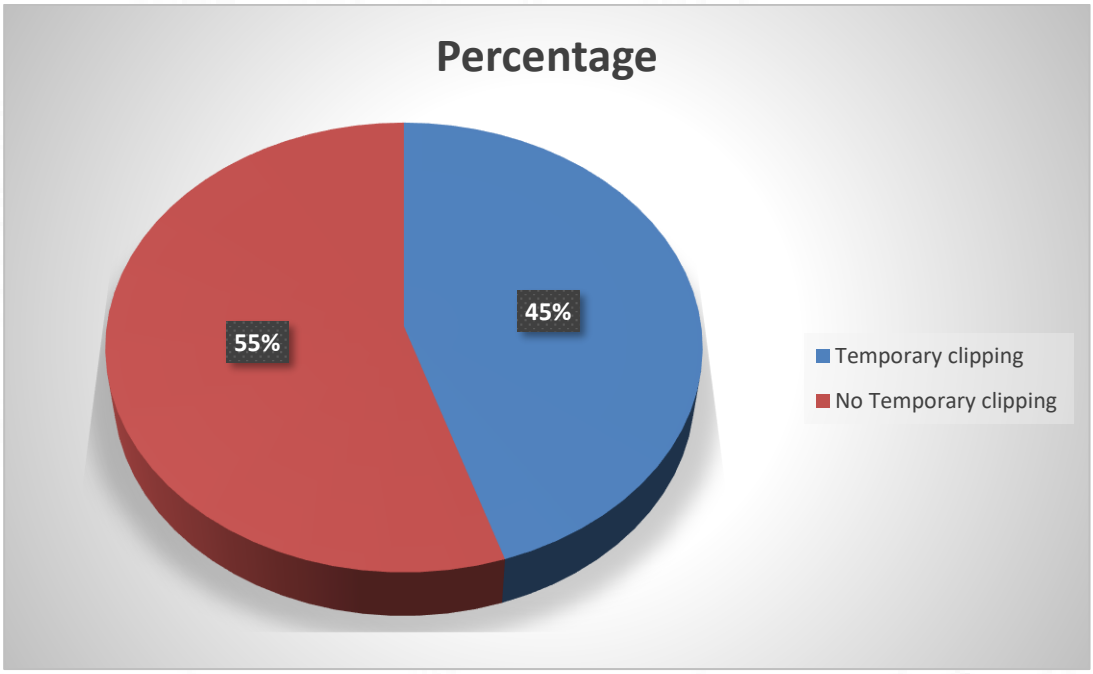
Table 7: Details of surgery done from the day of bleed [SAH]

Days from the bleed	Number of patients	Percentage[%]
Within I week	15	75

During II week	03	15
During III week	02	10

- Five patients had **intraoperative rupture** of the aneurysm.
- **Temporary Clipping :**

  Nine patients (45%) underwent temporary clipping on an average of 6.3 minutes, in the range of 2 minutes to 16 minutes.



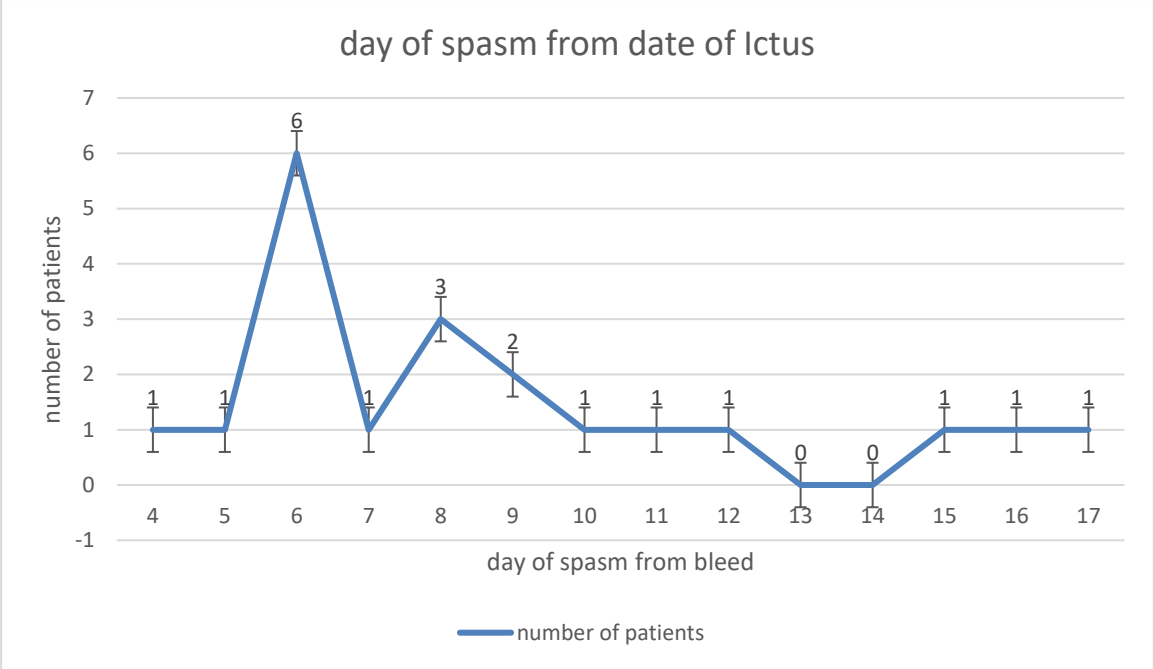
- Lamina terminalis was opened in thirteen patients (65%).

DETAILS OF VASOSPASM:

Day of vasospasm from the date of Ictus/ SAH :

All 20 patients developed vasospasm between 4 to 17 days from the date of ictus/ SAH.

On average each patient developed vasospasm, 8.75 days from the date of ictus.



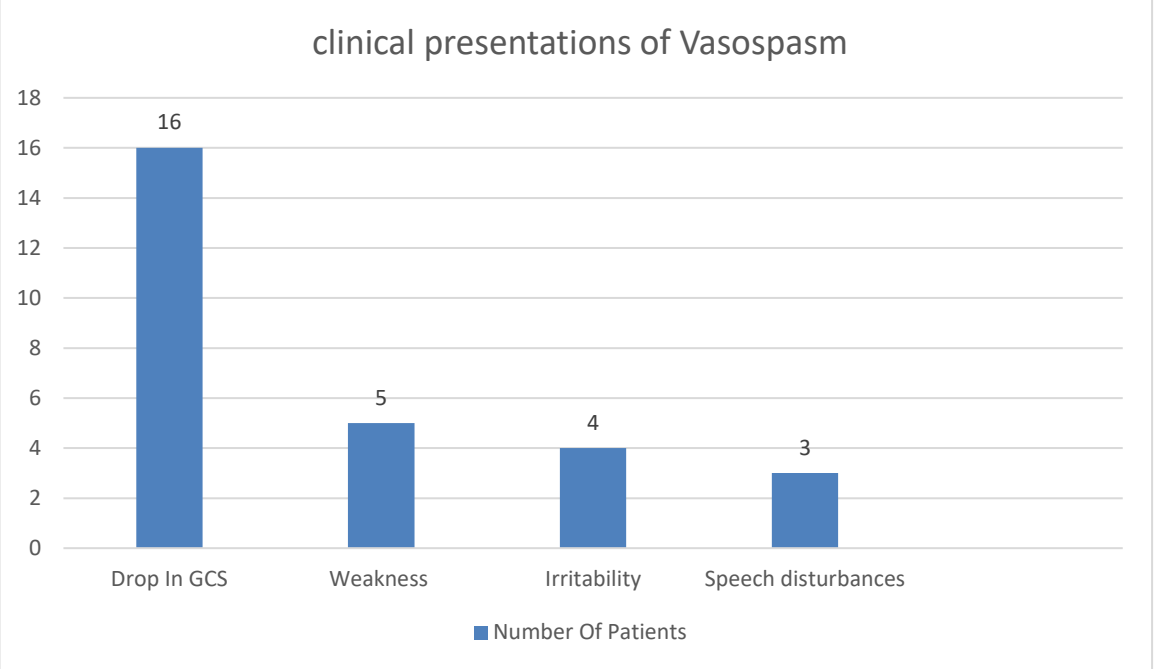
Indications for suspecting vasospasm:

Change in sensorium in form of drop-in sensorium was the most common presenting symptom in our study group. These patients upon a drop in GCS were subjected to digital subtraction angiography and upon confirmation, chemical angioplasty with milrinone was done.

Other presentations next to the drop in GCS were irrelevant talk, irritability, weakness, speech disturbances in form of slurring of speech/aphasia.

Table 8: Different clinical presentations of Vasospasm

Presentation	Number Of Patients
Drop In GCS	16
Weakness	05
Irritability	04
Speech disturbances	03



GCS score before undergoing Chemical angioplasty:

Patients had a GCS in between 6-14, when there was a drop in sensorium, before undergoing angioplasty. On average GCS dropped to 11.25.

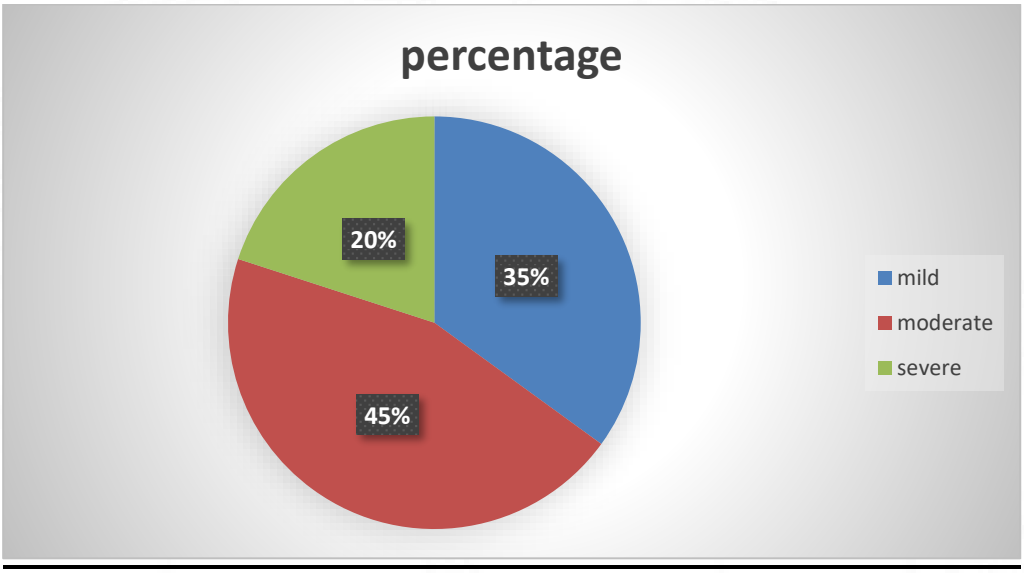
- These patients then underwent chemical angioplasty and were observed for clinical outcomes. In patients with a further drop in sensorium, non-improvement of symptoms was taken up for DSA and chemical angioplasty was performed upon confirmation of vasospasm. In patients where recurrent spasm was anticipated [based on either intraoperative picture, GCS drop, degree of vasospasm, or CT showing oedematous brain] sedation was continued and were electively ventilated. DSA was done to look for recurrent vasospasm.

Degree of spasm

Among 20 patients seven had mild degree spasm of the vessels, nine patients had the moderate degree and the rest of the four patients had a severe spasm.

Five patients had single-vessel narrowing and the rest of the patients had 2 or more vessel involvement. Twelve [60%] patients had a bilateral spasm of vessels.

Degree of spasm	Number of patients
Mild	07 [35%]
Moderate	09 [45%]
severe	04 [20%]



Sub Group Analysis:

- Patients were further grouped based on the number of angioplasties i.e. 1, 2, and 3 angioplasties.
- So, the effects of chemical angioplasty in the 3 groups were studied in each of the respective groups.

Degree of Vasospasm in patients who required single Chemical angioplasty:

A total of ten patients required only single chemical angioplasty. Among these ten patients, six(60%) were having mild spasms and the rest of the 4 were having moderate spasms.

Degree of Vasospasm inpatient who required Two Chemical angioplasties:

A total of seven patients required chemical angioplasty twice. Among these seven patients, five(71%) were having a moderate spasm and two were having a severe spasm.

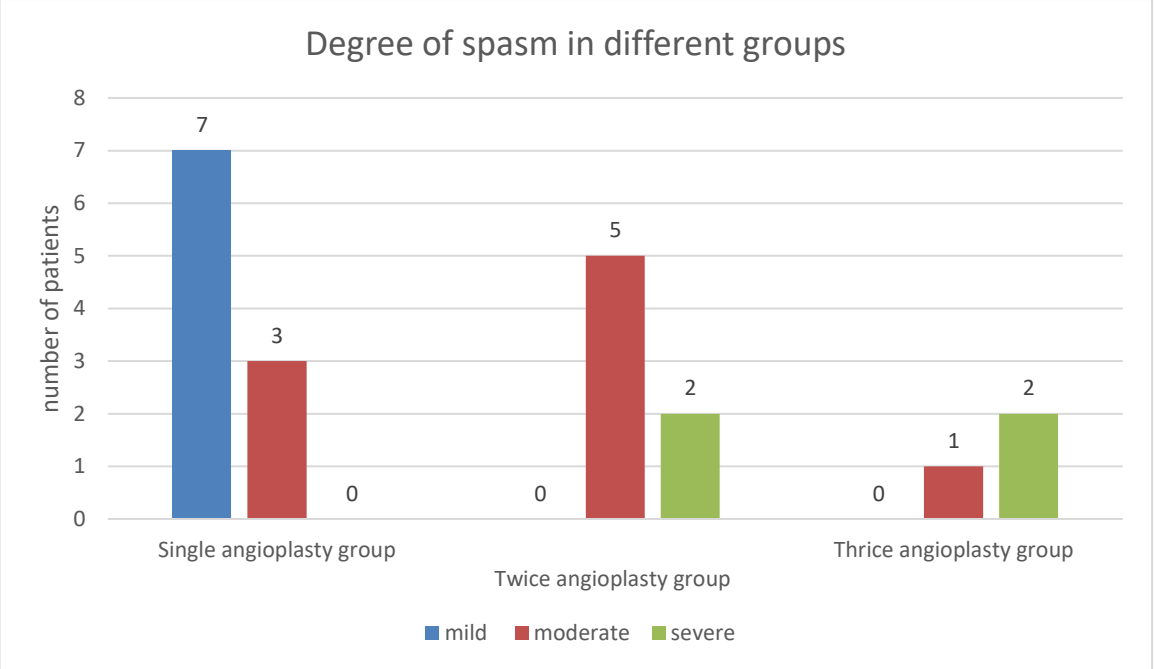
Degree of Vasospasm inpatient required three Chemical angioplasties:

Three patients required three times chemical angioplasty. Among these patients, two (67 %) has a severe spasm and one was having a moderate spasm.

These two patients with severe spasms were kept on elective ventilation and were weaned off ventilator support once three angioplasties were over and by that time they were subjected to balloon angioplasty.

Table 9- degree of vasospasm in different groups

Degree of vasospasm	Single angioplasty group	Twice angioplasty group	Thrice angioplasty group
Mild	07 [35%]	00	00
Moderate	03 [15%]	05 [25%]	01[5%]
Severe	00	02[10%]	02[10%]



Balloon Angioplasty:

Total four patients required balloon angioplasty. Two patients were from twice the angioplasty group and the other two from the thrice angioplasty group.

All these 4 patients had severe vasospasm which was resistant to milrinone infusion. Three patients had a partial response and the other patient did not have any effect on the vasospasm. So, ultimately these vasospastic territories were subjected to mechanical angioplasty.

Balloon angioplasty	Single angioplasty	Twice angioplasty	Thrice angioplasty
No. of patients	00	02 [29%]	02 [66%]

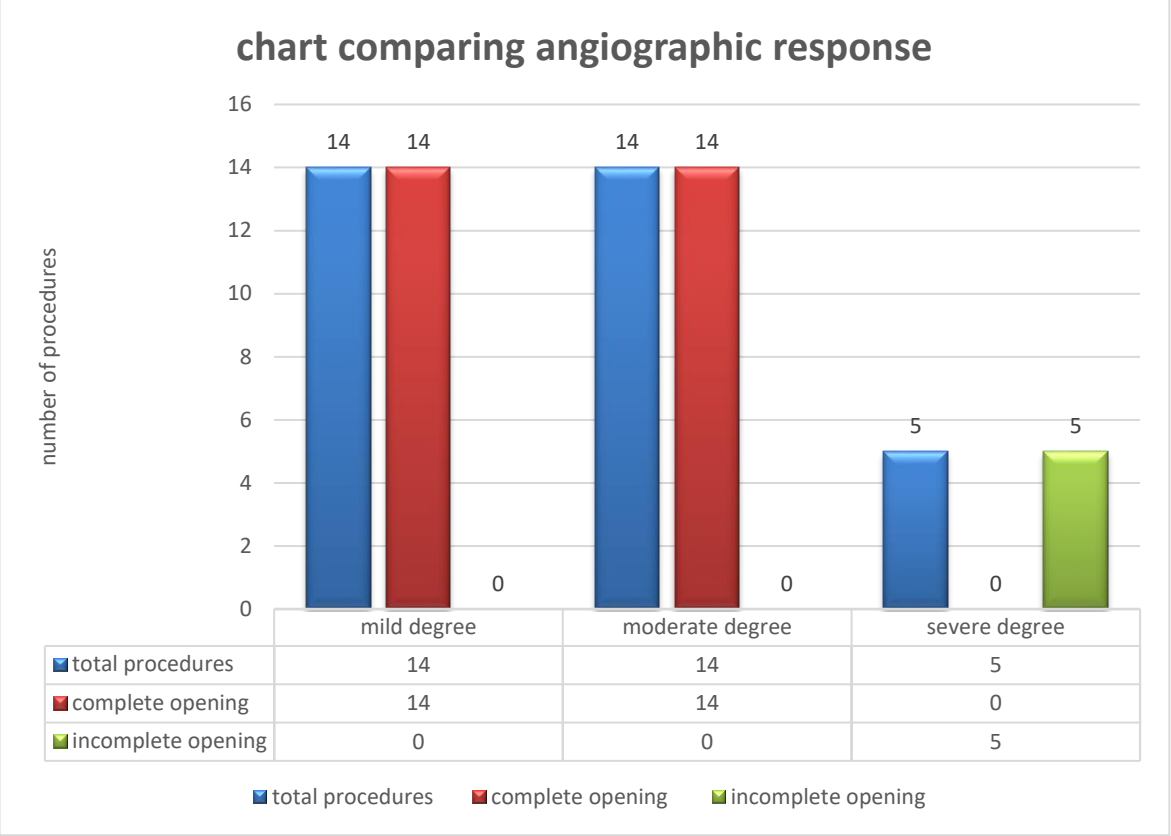
Angiographic response

Twenty patients with vasospasm underwent 33 angioplasty procedures, excluding those DSAs without evidence of spasm.

As already discussed 7 patients required two chemical angioplasties and 3 patients required three procedures. In four patients where milrinone infusion was inadequate to produce complete reversal, mechanical angioplasty was done.

Among these 33 procedures, 28 times milrinone infusion was able to reverse the vasospasm and resulted in the complete opening up of spastic vessels.

DEGREE OF SPASM	TOTAL PROCEDURES	COMPLETE OPENING	INCOMPLETE OPENING
MILD	14	14	00
MODERATE	14	14	00
SEVERE	5	0	5
	33	28	05
SPEARMANN'S CORRELATION			



Milrinone intraarterial infusion resulted in a total of 84% complete reversal of vasospasm. In the setting of severe spasms, this effect was seen, with 16% of procedures requiring mechanical angioplasty. This conveys a message regarding other factors playing a significant role in severe spastic segments and the need for further detailed studies.

There is a moderate negative correlation which was statistically significant i.e. with an increase in severity, the response will be reduced.

Also in this patient group, 12 [60%] patients had a bilateral spasm, which does not influence the reversible effects of milrinone. But half of these patients went on to require a second or third set of angioplasty or mechanical angioplasty. So bilateral spasms could be a predictor for recurrent vasospasm and they may require an additional dosage of infusion despite having a good angiographic response.

Circulation time:

In digital subtraction angiography, the circulation time is measured in each vasospastic segment, before infusion of milrinone and after infusion. The circulation time indirectly denotes cerebral perfusion, so improvements in circulation time are indicative of increased cerebral perfusion.

Cerebral circulation time of 3.5sec. or less was present in normal individuals.

A total of 43 large vessels in vasospasm and their territories were assessed for

In our study group mean circulation time pre-infusion was 4.5sec. [2.8-7.2 seconds]. After the minrin infusion circulation time on average improved to 4.09sec.[2.8 -5.6sec.] which indicated an increase in cerebral perfusion.

There was an improvement of circulation time in 21 [47%] vascular territories and in 17 [37%] territories, it was unchanged.

When statistically assessed, these improvements observed were statistically significant.

GCS outcome in the individual group:

There was a significant improvement in immediate GCS of patients who required angioplasty once or twice, also in those patients with mild or moderate degree spasm.

Angioplasty group	**GCS outcome**			
	Same GCS	Improved GCS	Drop In GCS	P Value
Single	01	09	00	**0.005**

Twice	01	05	01	0.343
Thrice	01	00	02	0.285
Total	03	14	03	**0.02**

- Wilcoxin signed Rank Test

The GCS improvement in the single angioplasty group reached a statistically significant value. Though there were patients with deterioration of sensorium in twice and thrice angioplasty groups, it was not statistically significant.

And, when overall GCS outcome among all groups was combined and compared, 70% of patients had improvement in GCS which was statistically significant.

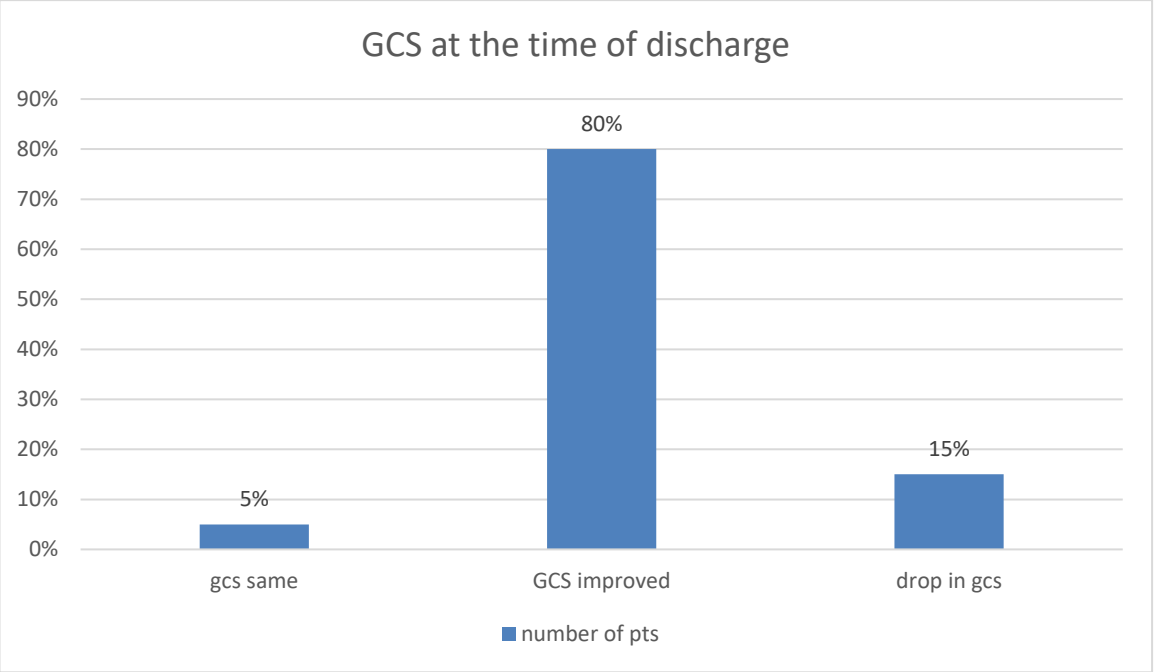
GCS at the time of Discharge:

Among 20 patients sixteen patients had a significant improvement in GCS at the time of discharge compared to pre angioplasty GCS.

	GCS same	GCS improved	Drop In GCS	p-value
Number of patients	01 [5%]	16 [80%]	03 [15%]	**0.02**

- Wilcoxin signed Rank Test

Among these 3 patients with drop-in GCS, 2 patients underwent thrice angioplasty and one underwent twice. All patients from single angioplasty had their GCS improved to 15, except one patient who had a GCS of 14.



Modified Rankin scale:

Modified Rankin scale [MRS] was assessed as a measure of functional outcome. Outcomes were noted at the time of discharge, 6 weeks and 3 months follow up periods.

MRS of 0-3 was considered a good functional outcome.

	Number of patients with MRS 0-3		
Angioplasty group	At Discharge	At 6 weeks	At 3 months

Single	4[20%]	9[45%]	10[50%]
Twice	1[5%]	2[10%]	5[25%]
Thrice	0	0	0
Spearman's Correlation			

Among the single angioplasty group, all patients [100%] reached good functional outcomes by the end of 3 month follow-up period and 8 out of 10 of them reached their pre rupture functional status, which was a good improvement.

But, neither of the patients who underwent three-time angioplasty could make out a good outcome. In the twice angioplasty group, 71% of patients achieved a good functional outcome.

Overall, 75% of patients achieving good functional outcomes at 3 months follow up period.

A statistically significant correlation was seen between the number of angioplasties required and the functional outcome score at 3 months, being more the angioplasties required the poorer the functional outcome, i.e. more the MRS score.

Degree of Spasm and MRS score :

All patients with mild vasospasm had good functional outcomes i.e. MRS score of 0-3.

In moderate degree vasospasm, MRS improvement was seen in 77% of patients. But, in severe degree of vasospasm, 75% of patients were expired at 3 months follow up period and the other one patient had MRS score of 4 at three months follow up.

Degree of vasospasm	Number of patients	MRS of [0-3] at 3 months
Mild	07	07[100%]
Moderate	09	07[77%]
Severe	04	00

Mortality :

No death happened during the hospital stay and at the time of discharge.

Three [15%] patients expired at 3 months follow-up period, whose MRS score was 5 at the time of discharge. All patients had a **severe spasm** and 2 of them received three angioplasties and the other patient had an infarct after the second angioplasty. All these 3 patients received balloon angioplasty after failed chemical angioplasty.

Infarct:

Six patients[30%] had an infarct in the computed tomography of the brain at the time of discharge.

Among which three patients had a severe spasm, two had a moderate spasm and one had a mild spasm.

So, Severe spasm denotes more chance of getting delayed cerebral ischemic events.

Degree of vasospasm	Number of patients	No. Of patients with Infarct
Mild	07	01[14%]
Moderate	09	02[22%]
Severe	04	03[75%]
Mann whitney U Test and P < 0.004		

The statistical analysis has shown significant relation between severity of vasospasm and development of infarct.

DISCUSSION

Vasospasm is one of the important complications of aneurysmal sub arachnoid hemorrhage which can cause significant morbidity and can lead to poor outcomes. Several treatment modalities were tried, but the search for definitive treatment is still on. Initially, patients were treated with triple H therapy [hemodilution, hypervolemia, and hypertension] in a belief that increasing circulatory volume will increase cerebral blood flow. But it was found that the effect was not seen clinically and besides it was associated with many complications related to volume overload. Now, only normovolemia with hypertension is recommended to prevent vasospasm.[117] Apart from triple H therapy, Mechanical angioplasty has been very effective to reverse vasospasm, often associated with a high chance of clinical improvement. But it was associated with many complications like rupture of untreated aneurysms, rupture of vessels, arterial dissection, and surgical clip displacement. So the usage of mechanical angioplasty should be based on assessing the risk-benefit ratio and used as an adjunct to the chemical angioplasty. Later many vasodilating agents have been tried through multiple routes of administration. Drugs like verapamil, papaverine, nimodipine, nicardipine, fasudil, and colforsin daropate have been tried. Only nimodipine had shown a promising role in the prevention of vasospasm.

Milrinone is a bipyridine methyl carbonitrile analog of amrinone. It acts by inhibiting the activity of phosphodiesterase III in vascular smooth muscle and increases the cytosolic cAMP. This leads to a reduction in calcium and so, less muscle contraction. It has a direct vasodilatory effect with inotropic action on the heart. Because of its inotropic action, it was initially used in patients with congestive heart failure. Later increased doses of milrinone were tried in canines, by Khajavi et al.,[114]

which established the effectiveness of high-dose milrinone in reversing vasospasm. This had led to human trials.

In 2001, Arakawa Y et al.[115] used milrinone infusion intraarterially and later intravenous infusions to treat vasospasm in seven patients and shown that milrinone was effective and safe to reverse vasospasm. This was the first study to use both intraarterial and intravenous routes.

The half-life of milrinone is 50 minutes. So, the effects of milrinone were short-lived. To prevent recurrent spasms, we need to maintain a steady-state concentration in blood. Intravenous milrinone infusions were introduced to overcome this problem and to maintain a steady concentration in blood. This infusion should be continued till there is a risk of vasospasm. Vasospasm occurs predominantly between 3-14 days from the initial rupture and SAH, it was advised to continue intravenous infusion till 14 days after the rupture of the aneurysm.
In this study, we tried to evaluate the effectiveness of milrinone infusion intraarterially and then intravenous infusion for 14 days.

Demographics: Among the 20 patients of the study group, the mean age was 55 years and 65% were females, which was comparable to the sex distribution of females, 68% of the study group in a study by Amanda Fraticelli et al.[116]

Clinical presentation: Sudden onset severe headache associated with vomiting was the most common presenting symptom. Loss of consciousness was also the next common presentation. No association between the loss of consciousness and GCS outcome was noted in our study. Also, it did not affect the MRS at the time of discharge [Mann Whitney U test]. Other symptoms being seizures, Speech disturbances, giddiness, altered sensorium, hemiplegia, and memory disturbances.

Risk factors: Hypertension is the most common risk factor and was present in 75% of patients. 20 % of the patients had a history of smoking. Both risk factors did not reach a statistically significant level.[Mann Whitney U test]

GCS at presentation: Majority (75%) had a GCS of 15, and only one patient had a GCS of 9 at the time of admission.
14 patients (70%) had a WFNS score of 1 at the time of admission, 5 patients had a grade of 2, and only one patient had a poor grade [WFNS 4].

We have observed a moderate positive correlation [higher the WFNS grade, higher the MRS] between WFNS grade and MRS at discharge, which was not statistically significant. Also the same was seen when compared with GCS at the time of discharge. A moderate negative correlation was seen between WFNS grade

at admission and GCS at the time of discharge, which was not statistically significant. [Spearman's correlation]

Location of aneurysm: Anterior communicating artery is the most common location of aneurysm in our study [55%]. Middle cerebral artery [20%], supra clinoid ICA[15%], anterior cerebral artery[5%], and basilar top aneurysms[5%] were in the order of frequency. The location of the aneurysm did not found to affect the vessel response or the clinical outcome in this study. [Kruskal -Wallis test]

Modified Fischer Grading: A total of 16 [80%] patients had thick SAH with the majority [45%] had an associated IVH. Among the rest of the 4 patients, two patients had a grade 1 and the other 2 patients had grade 2.

We have observed a weak positive correlation [higher the Fischer grade, higher the MRS] between Modified Fischer score and MRS at discharge, which was not statistically significant. Also the same was seen when compared with GCS at the time of discharge. A negligible negative correlation was seen between Modified Fischer score at admission and GCS at the time of discharge, which was not statistically significant. [Spearman's correlation]

Surgery from the date of bleed: 15 patients underwent clipping during the first week, three patients underwent in the second week, and the two others in the third week. Only two patients required more than one angioplasty when operated on during the second or third week. But the timing of surgery was not statistically significant when compared with either GCS or MRS at the time of discharge. [Spearman's correlation]

Intraoperative factors: Only 5 patients had intraoperative rupture of the aneurysm. Three of those five patients required two settings of angioplasty and two of them had infarct. But statistically intraoperative rupture did not affect GCS or MRS outcome. [Mann Whitney U test].

Nine patients [45%] required temporary clipping of proximal vessels before clipping of aneurysm. Regardless of the duration of clipping, five among these nine patients required more than two angioplasties, and three of these patients required balloon angioplasty subsequently. Among the nine patients who underwent temporary

clipping, five patients developed infarcts in the brain, which was statistically significant.

Degree of Vasospasm: 45% of patients had a moderate degree of vasospasm. 20% had severe vasospasm. Presence of moderate or severe vasospasm predicted recurrence or need for balloon angioplasty. This finding was correlated with Yasser et al.,[118] which found moderate or severe spasms predicted the need for rescue therapy.

Angiographic response: Twenty patients underwent a total of 33 DSA procedures, among which 28[84%] vascular territories responded well to the milrinone intraarterial infusion. These results were better than average response when compared to the systematic reviews.[3,119,120]

Study group	**Percentage of angiographic reversal**
Fraticelli et al.	90%
Lannes et al.	90%
Santos A G et al.	71%
Shankar et al.	84%
Our study	84%

Recurrence of Vasospasm: In our study ten patients [50%] required more than one angioplasty for recurrent vasospasm. This was relatively high when compared to the other studies.

In an initial study by Arakawa et al., 3 out of 7 patients[42%] required multiple angioplasties, whereas Fraticelli et al. reports 23% recurrence.

The number of angioplasties:

Our study reports seven patients requiring two settings of angioplasties and 3 [15%] patients requiring 3 times angioplasty procedure. This was comparable and even better compared to Arakawa et al. which had 28% of patients requiring three angioplasty procedures.

Balloon angioplasty: Patients who did not respond to milrinone infusion were subjected to mechanical or balloon angioplasty. In our study total of 4 patients[20%] required balloon angioplasty. All these patients had a severe degree of vasospasm. This was comparable with the number of balloon angioplasties in a study by Shankar et al. [123], it was reported as 21% in that study. Fraticelli et al. reported a 54% requirement of balloon angioplasty in their patient population.

Circulation time: There was a significant improvement in circulation time in our study. These results compared to studies by T. Iseda et al. and B. Turowski et al[78]., which also shown reductions in circulation time and increased cerebral perfusion. But both these studies used papaverine as an agent for infusion.

Our study is the first to describe circulation time changes with milrinone infusion.

Functional outcome/ MRS score: MRS score of 0-3 was taken as a good functional outcome. Though the GCS was improved in 80% of patients, discharge time MRS was not significantly improved. But, at 3 months follow up patients had a significant improvement in MRS score. This significant improvement was noted in 75% of the patient population in our study. This was 66% in a study by Shankar et al.[121] , 81% outcome was seen in Fraticelli group study. The systematic review by Lannes et al. reports an 80% good outcome. This outcome was correlated with the degree of vasospasm. None of the patients with severe grade vasospasm had shown good outcomes.

Suarez et al. [122]reported their one-third of patients required life-long care. In a review by Hop et al.[123] 10-20% of severe disability rates were seen.

Infarct: Patients were evaluated with computed tomography to see for the development of infarct in the vasospastic territories. Many patients develop infarcts remotely after some days after vasospasm. So, all patients were evaluated at the time of discharge and

during follow-up with computed tomography of the brain. 30% of patients developed infarcts in vasospastic segments in our study. Infarct rate was 21% in Yasser et al.

study and 7.1% in Lanne's systematic review. Vergouwen et al.[124] reported a 20% rate in patients with moderate to severe grade vasospasm. In our study, there was a statistically significant association found between the severity of vasospasm and the development of infarct.

Mortality rates: In this study group 15% of patients had mortality. Mortality happened in patients with poor MRS and GCS. These patients were discharged with poor MRS and died due to other systemic complications related to the poor MRS. These three patients had severe grade vasospasm in angiogram and required balloon angioplasty to reverse the vasospasm.

There is a paucity regarding the data on mortality rates. When compared to the other studies, Fraticelli reported 9% mortality and Shankar et al reported 7% mortality.

LIMITATIONS OF THE STUDY

- Small sample size

- Prospective- retrospective nature of the study. [As there was an outbreak of SARS COVID -19 during the study period, admissions of the patients got reduced and affected our study population]

- Variation in age and sex in both study group which may be confounding factor in our results.

- The short duration of follow-up. However, all patients are still under follow up and we are considering them for continuous evaluation during their follow-ups to diagnose long-term improvements in their MRS scores and complications if any.

- Lack of control group

- Inadequate dosing of milrinone in some patients of which may have confounded the results to some extent.

CONCLUSION

- Even in patients with WFNS grade 1 and 2, Vasospasm is one of the important complications in patients with aneurysmal subarachnoid hemorrhage

- Preoperative GCS and Modified Fischer Grade can predict the occurrence of cerebral vasospasm.

- Milrinone is safe to use and has not shown systemic side effects.

- Milrinone can be used effectively to reverse vasospasm in a mild and moderate degree of vasospasm. Milrinone's effectiveness in reversing vasospasm in these patients has been successfully confirmed with good functional improvements.

- Milrinone infusion also leads to significant improvements in circulation time, thereby improving cerebral perfusion.

- Patients resistant to chemical angioplasty, who subsequently underwent balloon angioplasty, had adverse clinical outcomes.
- In severe degree vasospasm, milrinone infusion alone may not suffice for adequate reversal of vasospasm and may require prior adjuvant treatment options like balloon angioplasty to prevent the development of drug tolerance.

- Patients with a severe degree of vasospasm are associated with poor functional outcomes and develop infarct in involved territories of the brain.

ANNEXURES

Sree Chitra Tirunal Institute for Medical Sciences & Technology

Proforma

Prospective retrospective observational study IMPACT OF CHEMICAL ANGIOPLASTY IN PATIENTS WITH VASOSPASM AND ANEURYSMAL SUBARACHNOID HEMORRHAGE IN PATIENTS ADMITTED UNDER NEUROSURGERY DEPARTMENT

General Instructions

Please fill in all the questions

Write Yes / No/NA wherever applicable

If the response is not known please write UK

If additional info is available please elaborate

Please use separate proforma for each admission

Intraoperative illustrations will be appreciated

Annexure I

Proforma

Title: Impact Of Chemical Angioplasty On patients with Subarachnoid Haemorrhage admitted under neurosurgery department.

Patient particulars-
Serial no
Age/sex
Education
Occupation
Diagnosis
D.O.A.
D. O. Surgery
D.O. Event

Chief complaint(s)

History of present illness

Past history

Treatment history

General examination

Systemic examination

Neurological Examination

Higher Functions

MMSE

Frontal assessment battery

Neuropsychological assessment

Cranial nerve assessment Right Left

Olfactory

Optic

	Right	Left
VA: Near Vision Far vision		
Visual field		

Fundus

CN III, IV & VI

Ocular movements

Pupils

Pupillary Reactions

Trigeminal nerve

Sensory

Motor

Corneal Reflex

Facial nerve

Vestibulocochlear nerve

CN IX &X

Uvula

Phonation

Palatal Movements

Gag Reflex

CN XI

CN XII

MOTOR EXAMINATION
- Bulk
- Tone
- Power

INVOLUNTARY MOVEMENTS
REFLEXES
- Deep Tendon Reflexes
- Superficial reflexes

Cerebellar signs

Sensory systems

Gait and stance

Skull and spine

Investigations
CT
- Size
- Location
- Bleed
- Others

MRI
- Size
- Location
- Other

CT Angiogram
- Size
- Arterial supply

DSA
- Size
- Aneurysm location
- Vasospasm

OTHER INVESTIGATIONS – blood investigations

SURGERY
- Approach
- Intraoperative finding

- Post-Op CT Scan
- Vitals- pulse rate/ respiratory rate/ blood pressure/ temperature
- Serum Electrolytes

Postoperative Neurological status
--Immediate
--During the event

--Immediately after chemical angioplasty

--During Any further Events

Any Other Post-Operative Complications
-TCD velocities- before and after chemical angioplasty
After Chemical Angioplasty-
1.GCS
2.Focal deficits
3.CT changes
4.IN DSA- i) Degree of stenosis
ii) territory involved
iii) circulation time
5.Effect of angioplasty [on change in sensorium i.e. GCS / focal deficits] lasted for [duration]-in hours
6.number of patients needed mechanical angioplasty

Follow up

Sl no	POD	MODIFIED RANKIN SCORE	Neurological Status	DSA
1				
2				
3				

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
(An Institution of National Importance, Department of Science and Technology, Government of India)
टेलीफोन नं./Telephone No.: 0471-2443152 फैक्स/Fax: 0471-2446433, 2550728
ई-मेल/E-mail: sct@sctimst.ac.in वेबसाइट/Website: www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1589/DECEMBER-2020 19.12.2020

Dr.Gowtham M,
Senior Resident,
Dept of Neurosurgery,
SCTIMST, Thiruvananthapuram

Dear Dr. Gowtham M,

Thank you for submitting documents related to your proposal titled "**IMPACT OF CHEMICAL ANGIOPLASTY ON PATIENTS WITH VASOSPASM AND SUBARACHNOID HAEMORRHAGE ADMITTED UNDER NEUROSURGERY DEPARTMENT** (IEC/1589)" to the IEC for review.

The following documents were reviewed:

1. Check list
2. Covering letter addressed to Chairperson, IEC, SCTIMST dated 28.08.2020 by the PI
3. Covering letter addressed to Chairman, IEC, SCTIMST by Dr. Mathew Abraham (Guide)
4. TAC Approval Letter
5. Singed IEC Application Form
6. Proforma
7. Project Proposal
8. Patient Information Sheet (English)
9. Patient Information Sheet (Malayalam)
10. Consent Form(English)
11. Consent Form(Malayalam)
12. Signed CV of Dr. Gowtham M with APMC Registration number
13. Signed CV of Dr. Mathew Abraham with TCMC Number
14. Signed CV of Dr. Jayadevan with TCMC Number

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 23-October 29, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Plagiarism Checker X Originality Report

Similarity Found: 5%

Date: Aug 9, 2021
Statistics: 434 words Plagiarized / 9463 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.

‘ **a high correlation between the presence of** blood in subarachnoid cisterns in CT scan

Modified Fisher scale and risk for vasospasm Focal **or diffuse thin layer of SAH**, IVH present: carries moderate risk for vasospasm 3-Focal **or diffuse thick layer of SAH**, no IVH: carries high risk for vasospasm 4-Focal **or diffuse thick layer of SAH**, IVH present

most effective means of detecting early ischemia. Patients can have diminished attention, changes in verbal output, or a new pronator drift of the upper extremity, which are easy to be missed by beginners.

Posterior territory **vasospasm can cause more generalized neurological deterioration.**

TCD is effective in detecting **1proximal vasospasm because of segmental and diffuse increases in blood flow velocity in these vessels** when compared with more distally located vessels.57 There is a **good general correlation between TCD velocities and** development vasospasm. TCD **velocities in the MCA greater than 120 cm/second are indicative of some degree of vasospasm and** velocities greater than 200 cm/second, are consistent with severe vasospasm.
MICRODIALYSIS It is **1measurement of extracellular concentrations of glutamate, lactate, pyruvate, glucose, and glycerol in brain tissue.**

References:

[1] Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2010;41:e519–e536

[2]Diringer MN, Bleck TP, Claude Hemphill J III, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the neurocritical care society's multidisciplinary consensus conference. Neurocrit Care. 2011;15:211–240.

[3] Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/ american Stroke Association. Stroke. 2012;43:1711–1737

[4] Thibaud Crespy, MD, et al. Which Protocol for Milrinone to Treat Cerebral Vasospasm Associated With Subarachnoid Hemorrhage? from the J Neurosurg Anesthesiol 2018;

[5] Arakawa Y, Kikuta K, Hojo M, et al. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. Neurosurgery. 2001;48:723–728

[6]Neurosurgery clinics of North America:Vol.1,No.2, April 1990: 265p-276p.

[7]Rtorey H: Microscopical observations on the circulation of blood in the cerebral cortex. Brain 48: 45p-64p.

[8] Zucker MB: A study of the substances in blood serum and platelets which stimulate smooth muscle. Am J Physiol 14iI:12—26, 1B44.

[9] Jackson IJ: Aseptic hemogenic meningitis :An experimental study of aseptic meningeal reactions due to blood and its breakdown products.Arch Neurol.Psychiatry1949: 62: 572p-589p.

[10] Eeker A, Riemensehneider PA: Arteriographic demonstration of spasm of the intracianlal arteries with special reference to saccular arterial aneurysms. **1851** J Neurosurg 8:660p-807p.

[11] Denny-Brown D: The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm," Med Clin North Am :1951: 35:1457-1474.

[12]Stornelli SA, French JD: Subarachnoid hemorrhage—factors in prognosis and management. J Neurosurg 1964: 21:769—780.

[13] Allcock JM, Drake CG: Ruptured intra cranial aneurysms and the role of arterial spasm. J Neuro Surg 1965:22:21p-29p.

[14] Kennady JC: Investigations of the early fate and removal of subarachnoid blood. Pacific Med Surg 75:163-168, 1967

[15] Simeone FA, Ryan KG, Cotter JR: Prolonged experimental cerebral vasospasm. J Neurosurg 29: 35Y—366, 1968

[16] Suzuki J, Takaku A, Suzuki S, et al: Prognostic correlation with cerebral vasospasm and the operation for the intracranial aneurysm. Brain Nerve 22:1261— 1267, 1970

[17] SuZuki J, Yoshimoto T: Early operation for rup tured intracranial aneurysm.-especially the cases operated within 48hrs after the last subarachnoid hemorrhage. J Surg 3:149- 156, 1973

[18]Wice G, Sutter R, Burkholdei J: The treatment of brain ischemia with vasopressor drugs. Stroke **3:135—140, 1972**

[19] Wernick S, Sugar O: Treatment of postangiographic hemiplegia with vasopressors. J Neurosurg 41:755—767, 1974.

[20] Saito I, Ueda Y, Sano K: Significance of vasospasm in the treatment of ruptured intracranial aneurysm**.** J Neurosurg 47:412—429, 1877.

[21] Osaka K: Prolonged vasospasm produced by the breakdown products of erythrocytes. J Neurosurg 47:40 11, 1977

[22] Takemae T, Mizukami M, Kim H, et al: Computed tomography of ruptured intracranial aneurysms in acute stage—relationship between vasospesna arid high density on CT scan. Brain Nerve 30.861—866, 1978

[23] Sasaki T, ASano T, Sano K: Cerebral vasospasm and free radical reactions. Neurol Med Chir 20:145— 153, 1980

[24] Fisher CM, Kistler JP, Davis JM: Relation of cerebral vaaospasm to subarachnoid hemorrhage visualized by computerized tomographic scaning. Neurnsurgery 69:723-735, 1980

[25] Takahashi S, Sonobe M, Nagamine Y: Early operations for ruptured intracranial aneurysm-comparative study with computed tomography. ActaNeurochir 1981:57:23p-31p

[26] Dorsch NWC, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage: I. Incidence and effects. J Clin Neurosci. 1994;1:19-26.

[27] Dorsch NWC, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage: I.

Incidence and effects. J Clin Neurosci. 1994;1:19-26.
[28] Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke. 1994;25:1342-7.
[29] Friedman JA, Goerss SJ, Meyer FB, et al. Volumetric quantification of Fisher grade 3 aneurysmal subarachnoid hemorrhage: a novel method to predict symptomatic vasospasm on admission computerized tomography scans. J Neurosurg. 2002;97:401-7.

[30] Kramer AH, Hehir M, Nathan B, et al. A comparison of 3 radiographic scales for the prediction of delayed ischemia and prognosis following subarachnoid hemorrhage. J Neurosurg.

[31] Reilly C, Amidei C, Tolentino J, Jahromi BS, MacDonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2004;101:255-61.

[32] Harrod CG, Bendok BR, Batjer HH. Prediction of cerebral vasospasm in patients presenting with aneurysmal subarachnoid hemorrhage: a review. Neurosurgery. 2005;56:633-54.

[33] de Rooij N, Rinkel G, Danbaar J, Frijins CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. Stroke. 2013;44:43-54.

[34] Abla A, Wilson D, Williamson R, et al. The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. J Neurosurg. 2014;120:391-7.
[35] Conway JE, Tamargo RJ. Cocaine use is an independent risk factor for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2001;32:2338-43.
[36] Schwartz TH, Solomon RA. Perimesencephalic nonaneurysmal subarachnoid hemorrhage: review of the literature. Neurosurgery. 1996;39:433-40.
[37] Rabinstein AA, Pichelmann MA, Friedman JA, et al. Symptomatic vasospasm and outcomes following aneurysmal subarachnoid hemorrhage: a comparison between surgical repair and endovascular coil occlusion. J Neurosurg. 2003;98:319-25.

[38] Sheth S, Hausrath D, Numis A, Lawton MT, Jospehoson SA. Intraoperative rerupture during surgical treatment of aneurysmal subarachnoid hemorrhage is not associated with an increased risk of vasospasm. J Neurosurg. 2014;120:409-14

[39] . Orite F, Mink S, Tan C, et al. Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. Stroke. 2014;45:677-82.

[40] Koide M, Nishizawa S, Ohta S, Yokoyama T, Namba H. Chronological changes of the contractile mechanism in prolonged vasospasm after subarachnoid hemorrhage: from protein kinase C to protein tyrosine kinase. Neurosurgery. 2002;
51:1468-76

[41] Findlay JM, Weir BKA, Kanamaru K, Espinosa F. Arterial wall changes in cerebral vasospasm. Neurosurgery. 1989;25:736-46.

[42] Sasaki T, Wakai S, Asano T, Watanabe T, Kirino T, Sano K. The effect of a lipid hydroperoxide of arachidonic acid on the canine basilar artery: an experimental study on cerebral vasospasm. J Neurosurg. 1981;54:357-65.
[43] Foley PL, Takenaka K, Kassell NF, Lee KS. Cytotoxic effects of bloody cerebrospinal fluid on cerebral endothelial cells in culture. J Neurosurg. 1994;81:87-92.

[44] Iuliano BA, Pluta RM, Jung C, Oldfield EH. Endothelial dysfunction in a primate model of cerebral vasospasm. J Neurosurg. 2004;100:287-94.

[45] Moon CT, Gajdusek C, London S, Mayberg MR. Expression of endothelial nitric oxide synthase after

exposure to perivascular blood. Neurosurgery. 2001;48:1328-34.

[46] Chow M, Dumont AS, Kassell NF. Endothelin receptor antagonists and cerebral vasospasm: an update. Neurosurgery. 2002;51: 1333-42.

[47] Seifert V, Löffler BM, Zimmermann M, Stolke D. Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage: correlation with cerebral vasospasm, delayed ischemic neurological deficits, and volume of hematoma. J Neurosurg. 1995;82:55-62.

[48] Dumont AS, Dumont RJ, Chow MM, et al. Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. Neurosurgery. 2003;53:123-35.

[49] Sasaki T, Kasuya H, Onda H, et al. Role of p-38 mitogen–activated protein kinase on cerebral vasospasm after subarachnoid hemorrhage. Stroke. 2004;35:1466-70.

[50] . Clatterbuck RE, Gailloud P, Ogata L, et al. Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates. J Neurosurg. 2003;99:376-82. 48. Pradilla G, Wang PP, Legnani RG, Frazier JL, Tamargo RJ. Prevention of vasospasm by anti-CD11/CD18 monoclonal antibody therapy following subarachnoid hemorrhage in rabbits. J Neurosurg. 2004;101:88-92.

[51] Mocco J, Mack WJ, Kim GH, et al. Rise in serum soluble intercellular adhesion molecule-1 levels with vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;97: 537-41.

[52] Schoch B, Regel JP, Wichert M, Graser T, Vollbracht L, Stolke D. Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. Neurosurgery. 2007;60:828-36.

[53] Rowland M, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315-29.

[54] Sanchez-Porras R, Zheng Z, Santos E, Scholl M, Unterberg AW, Sakowitz OW. The role of spreading depolarization in subarachnoid hemorrhage. Eur J Neurol. 2013;20:1121-7.

[55] Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm—the clinical manifestations. Neurosurgery. 1977;1:245-58.

[56] Rowland M, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth. 2012;109(3):315-29.

[57] Sanchez-Porras R, Zheng Z, Santos E, Scholl M, Unterberg AW, Sakowitz OW. The role of spreading depolarization in subarachnoid hemorrhage. Eur J Neurol. 2013;20:1121-7.

[58] Purkayastha S, Sorond F. Transcranial doppler ultrasound: Technique and application. Semin Neurol. 2012;32(4):411-20.

[59] Lindegaard KF, Bakke SJ, Sorteberg W, Nakstad P, Nornes H. A non-invasive Doppler ultrasound method for the evaluation of patients with subarachnoid hemorrhage. Acta Radiol. 1986;369: 96-8.

[60] Sviri GE, Ghodke B, Britz GW, et al. Transcranial Doppler grading criteria for basilar artery vasospasm. Neurosurgery. 2006;59: 360-6.

[61] Lysakowski C, Walder B, Costanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm. A systematic review. Stroke.2001;32:2292-8.

[62] Ratsep T, Asser T. Cerebral hemodynamic impairment after aneurysmal subarachnoid hemorrhage as evaluated using transcranial Doppler ultrasonography: relationship to delayed cerebral ischemia and clinical

outcome. J Neurosurg. 2001;95:393-401.

[63] Okada Y, Shima T, Nishida M, et al. Comparison of transcranial Doppler investigation of aneurysmal vasospasm with digital subtraction angiographic and clinical findings. Neurosurgery. 1999;45:443-50.

[64] Egge A, Sjoholm H, Waterloo K, Solberg T, Ingebrigsten T, Romner B. Serial single-photon emission computed tomographic and transcranial Doppler measurements for evaluation of vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2005;57:237-42.

[65] . Minhas PW, Menon DK, Smielewski P, et al. Positron emission tomographic cerebral perfusion disturbances and transcranial Doppler findings among patients with neurological deterioration and subarachnoid hemorrhage. Neurosurgery. 2003;52:1017-24

[66] Hertel F, Walter C, Bettag M, Mosdorf M. Perfusion-weighted magnetic resonance imaging in patients with vasospasm: a useful new tool in the management of patients with subarachnoid hemorrhage. Neurosurgery. 2005;56:28-35.

[67] Weidauer S, Lanfermann H, Raabe A, Zanella F, Seifert V, Beck J. Impairment of cerebral perfusion and infarct patterns attributable to vasospasm after aneurysmal subarachnoid hemorrhage. A prospective MRI and DSA study. Stroke. 2007;38:1831-6.

[68] Sviri GE, Britz GW, Lewis DH, Newell DW, Zaaroon M, Cohen W. Dynamic perfusion computed tomography in the diagnosis of cerebral vasospasm. Neurosurgery. 2006;59:319-25.

[69] Washington C, Zipfel G. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. Neurocrit Care. 2011;15:312-7.

[70] Zweifel C, Castellini G, Czosnyka M, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. Stroke. 2010;41(9): 1963-8.

[71] Yokose N, Sakatani K, Murata Y, et al. Bedside monitoring of cerebral blood oxygenation and hemodynamics after aneurysmal subarachnoid hemorrhage by quantitative time-resolved nearinfrared spectroscopy. World Neurosurg. 2010;73(5):508-13.

[72] Spiotta A, Provencio J, Rasmussen P, Manno E. Brain monitoring after subarachnoid hemorrhage: lessons learned. Neurosurgery. 2011;69:755-66.

[73] Otawara Y, Ogasawara K, Ogawa A, Sasaki M, Takahashi K. Evaluation of vasospasm after subarachnoid hemorrhage by use of multislice computed tomographic angiography. Neurosurgery. 2002;51:939-43.

[74] Hattingen E, Blasel S, DuMesnil R, Vatter H, Zanella Fe, Weidauer S. MR angiography in patients with subarachnoid hemorrhage: adequate to evaluate vasospasm-induced vascular narrowing. Neurosurg Rev. 2010;33:431-9.

[75] Washington C, Zipfel G. Detection and monitoring of vasospasm and delayed cerebral ischemia: a review and assessment of the literature. Neurocrit Care. 2011;15:312-7.

[76] Grietz T. Normal cerebral circulation time as determined by carotid angiography with sodium and methylglucamine diatrizoate [urograffin]. Acta Radiol (Diagn)(Stockholm)1968;7:P331-336.

[77] B.Turowski et al. Assessment of changes in cerebral circulation time due to vasospasm in a soecific arterial territory: effect of angioplasty. Neuroradiology.(2005) 47:p 134-143.

[78] Nakagawa A, Su CC, Sato K, Shirane R. Evaluation of changes in circulating blood volume during acute and very acute stages of subarachnoid hemorrhage: implications for the management of hypovolemia. J

Neurosurg. 2002;97:268-71.

[79] Lennihan L, Mayer SA, Fink ME, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. Stroke. 2000;31:383-91.
[80] Rinkel GJE, Feigin VL, Algra A, van Gijn J. Hypervolemia in aneurysmal subarachnoid hemorrhage. Stroke. 2005;36:1104-5.
[81] Suarez JI, Shannon L, Zaidat OO, et al. Effect of human albumin administration on clinical outcome and hospital cost in patients with subarachnoid hemorrhage. J Neurosurg. 2004; 100:585-90.
[82] McGirt MJ, Blessing R, Nimjee SM, et al. Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurosurgery. 2004;54:1369-74.
[83] Mori T, Katayama Y, Kawamata T, Hirayama T. Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisones in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 1999;91:947-52.
[84] Smith MJ, Le Roux PD, Elliott JP, Winn HR. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. J Neurosurg. 2004;101:1-7.
[85] Dorhout Mees SM, Rinkel GJE, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid hemorrhage. Stroke. 2009;39:514-5.
[86] Zwienenberg-Lee M, Hartman J, Rudisill N, et al. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage. Results of a phase II multicenter, randomized, clinical trial. Stroke. 2008;39:1759-65.
[87] Amin-Hanjani S, Ogilvy CS, Barker FG 2nd. Does intracisternal thrombolysis prevent vasospasm after aneurismal subarachnoid hemorrhage? A meta-analysis. Neurosurgery. 2004;54:326-35.
[88] Andaluz N, Zuccarello M. Fenestration of the lamina terminalis as a valuable adjunct in aneurysm surgery. Neurosurgery. 2004;55: 1050-9.
[89] Kasuya H, Onda H, Sasahara A, Takashita M, Hori T. Application of nicardipine prolonged-release implants: analysis of 97 consecutive patients with acute subarachnoid hemorrhage. Neurosurgery. 2005;56:895-902.
[90] Dalbasti T, Karabiyikoglu M, Ozdamar N, Oktar N, Cagli S. Efficacy of controlled-release papaverine pellets in preventing symptomatic cerebral vasospasm. J Neurosurg. 2001;95:44-50.
[91] Barth M, Capelle H, Weidauer S, et al. Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study. Stroke. 2007;38:330-6.
[92] Golan E, Vasquez D, Ferguson N, Adhikari NK, Scales DC. Prophylactic magnesium for improving neurologic outcome after aneurysmal subarachnoid hemorrhage: systematic review and meta-analysis. Journal of Critical Care. 2013;28:173-81.
[93] Shaw MDM, Vermeulen V, Murray GD, Pickard JD, Bell BA, Teasdale GM. Efficacy and safety of the endothelinA/B receptor antagonist TAK-044 in treating subarachnoid hemorrhage: a report by the Steering Committee on behalf of the IK/Netherlands/ Eire TAK-044 Subarachnoid Haemorrhage Study Group. J Neurosurg. 2000;93:992-7.
[94] Su S, Xu W, Hai J, Wu YF, Yu F. Effects of statins-use for patient with aneurysmal subarachnoid hemorrhage: a meta-analysis of randomized controlled trials. Sci Rep. 2014;4:4573.
[95] Wong GK, Chan DY, Siu DY, et al. High-dose Simvastatin for aneurysmal subarachnoid hemorrhage: multicenter randomized controlled double-blinded clinical trial. Stroke. 2015;46:382-8.
[96] Raabe A, Beck J, Keller M, Vatter H, Zimmermann M, Seifert V. Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg. 2005; 103:974-81.
[97] Meyer R, Deem S, Yanez N, Souter M, Lam A, Treggiari MM. Current practices of triple-h prophylaxis and therapy in patients with subarachnoid hemorrhage. Neurocrit Care. 2011;14:24-36.
[98] Egge A, Waterloo K, Sjøholm H, Solberg T, Ingebrigtsen T, Romner B: Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. Neurosurgery 2001; 49: 593–605, discussion 605–606.
[99] Treggiari MM, Deem S: Which H is the most important in triple-H therapy for cerebral vasospasm- Curr Opin Crit Care 2009; 15: 83–86.
[100] Rinkel GJ, Feigin VL, Algra A, van Gijn J: Circulatory volume expansion therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev 2004; 4:CD000483.
[101] Naidech AM, Jovanovic B, Wartenberg KE, Parra A, Ostapkovich N, Connolly ES, Mayer SA, Commichau

C: Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. Crit Care Med 2007; 35: 2383–2389.
[102] Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, Quintel M, Schmiedek P, Vajkoczy P: Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue
oxygenation after subarachnoid hemorrhage. Crit Care Med 2007; 35: 1844–1851, quiz 1852.
[103] Sayama CM, Liu JK, Couldwell WT: Update on endovascular therapies for cerebral vasospasm induced by aneurysmal
subarachnoid hemorrhage. Neurosurg Focus 2006; 21:E12.
[104] Kaku Y, Yonekawa Y, Tsukahara T, Kazekawa K: Superselective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg 1992; 77: 842–847.
[105] Sawada M, Hashimoto N, Tsukahara T, Nishi S, Kaku Y, Yoshimura S: Effectiveness of intra-arterially infused papaverine solutions of various concentrations for the treatment of cerebral vasospasm. Acta Neurochir (Wien) 1997; 139: 706–711.
[106] McAuliffe W, Townsend M, Eskridge JM, Newell DW, Grady MS, Winn HR: Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. J Neurosurg 1995; 83: 430–434.
[107] Hui C, Lau KP: Efficacy of intra-arterial nimodipine in the treatment of cerebral vasospasm complicating subarachnoid haemorrhage. Clin Radiol 2005; 60: 1030–1036.
[108] Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, van Effenterre R: Intra-arterial nimodipine
for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. AJNR Am J Neuroradiol 2004; 25: 1067–1076.
[109] Bayer HealthCare: Important drug warning, February 2006.
[110] Conti A, Angileri FF, Longo M, Pitrone A, Granata F, la Rosa G: Intra-arterial nimodipine to treat symptomatic cerebral vasospasm following traumatic subarachnoid haemorrhage: technical case report. Acta Neurochir (Wien) 2008; 150: 1197–1202, discussion 1202.

[111] Kim JH, Park IS, Park KB, Kang DH, Hwang SH: Intraarterial nimodipine infusion to treat symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Korean Neurosurg Soc 2009; 46: 239–244
[112] Honerjäger P: Pharmacology of bipyridine phosphodiesterase III inhibitors. Am Heart J 1991; 121: 1939–1944.

[113] Khajavi K, Ayzman I, Shearer D, Jones SC, Levy JH, Prayson RA, Skibinski CI, Hahn JF, Chyatte D: Prevention of chronic cerebral vasospasm in dogs with milrinone. Neurosurgery 1997; 40: 354–363.

[114] Arakawa Y, Kikuta K, Hojo M, Goto Y, Ishii A, Yamagata S: Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. Neurosurgery 2001; 48: 723–728, discussion 728–730.

[115] Amanda Fraticelli T, Cholley BP, Losser MR, Saint Maurice JP, Payen D: Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 2008; 39: 893–898.

[116] Arakawa Y, Kikuta K, Hojo M, Goto Y, Yamagata S, Nozaki K, Hashimoto N: Milrinone reduces cerebral vasospasm after subarachnoid hemorrhage of WFNS grade IV or V. Neurol Med Chir (Tokyo) 2004; 44: 393–400.

[117]Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43(6):1711-37.

[118] Yasser B. Abulhasan. Milrinone for refractory cerebral vasospasm with delayed cerebral ischemia: J Neurosurg.march,2020.P1-12
[119] Alex Goes Santos-Teles et al. Efficacy and safety of milrinone in the treatment of .cerebral vasospasm after subarachnoid hemorrhage: a systematic review

[120] Marcelo Lannes et al. The Use of Milrinone in Patients with Delayed Cerebral Ischemia Following Subarachnoid Hemorrhage: A Systematic Review : Can J Neurol Sci. 2017; 44: 152-160

[121] JJS shankar et al. Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology 2011: 53:123–128

[122] Suarez JI et al. Aneurysmal subarachnoid hemorrhage. *N Engl J Med.* 2006;354:P387–396.

[123] Hop JW, et al.. Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. *Stroke*. 1997;28:660–664.

[124] Vergouwen MD, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke*. 2011;42(4):924–929.