

INTERVENTIONAL MANAGEMENT OF INTRACRANIAL ARTERIO-VEINUS MALFORMATIONS

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Abstract: Arteriovenous Malformations (AVMs) are a complex network of abnormal vascular channels that consist of arterial feeders, arterial collaterals, the AVM nidus and the enlarged venous outflow channels. All AVMs have three components a) feeding arteries; b) nidus and c) draining vein. Majority of the symptoms of AVMs are due to abnormal hemodynamic situation causing hemorrhage, seizure or increasing neurological deficit. More than 50% of AVMs present with spontaneous intracranial hemorrhage. Intracerebral hemorrhage occurs more commonly, although subarachnoid hemorrhage and intraventricular hemorrhage can also occur. The possible sites of hemorrhage in AVMs include nidus, proximal arterialized vein, intranidal aneurysm and feeding artery aneurysm. The goal of treatment is complete obliteration of nidus to get the cure. The pre-procedural imaging in Cerebral AVMS relies on Digital Subtraction Angiography (DSA), which is still the gold standard for diagnosis and management. CT demonstrates serpiginous iso or hyperdense tangled mass of vessels which show intense enhancement. There may be evidence of hemorrhage, calcification, gliotic scar and ischemic changes in the surrounding brain. MRI and MRA are superior to CT in demonstrating the topography of the AVM. MR is more accurate than CT in determining the overall size of the nidus. It is also better suited to demonstrate subacute and chronic hemorrhage and secondary changes in the adjacent brain. Spetzler and Martin Grading of AVMs is based on size, location and deep venous drainage.

The treatment options for cerebral AVMs include Surgical excision, Endovascular embolization, Stereotactic radiotherapy or a combination of above. The current understanding of hemodynamics of AVM is focused on 'nidus', with endovascular embolization aimed at its obliteration. Surgery is generally done as an elective procedure. The factors to be considered for surgical excision of cerebral AVM includes: location, type of lesion, larger sized malformation. Stereotactic Radiotherapy irradiates blood vessels of the AVM to cause progressive luminal obliteration & thereby preventing hemorrhage. A multidisciplinary approach provides the best outcome.

Key Words : Arteriovenous Malformations (AVMs): Nidus: Endovascular embolization

INTRODUCTION

Arteriovenous Malformations (AVMs) are a complex network of abnormal vascular channels that consist of arterial feeders, arterial collaterals, the AVM nidus and the enlarged venous outflow channels. Presence of a shunt between the arterial and the venous system is essential for diagnosis. All AVMs have three components a. Feeding arteries b. Nidus c. Draining Vein. Intracranial arteriovenous malformations (AVMs) are generally of two types I. AVM with plexiform Nidus – A collection of multiple small vessels with AV Shunt. II. A fistula- A single direct communication between one artery & vein. Approximately 83% to 93% AVMs are supratentorial.

Majority of the symptoms of AVMs are due to abnormal hemodynamic situation causing hemorrhage, seizure or increasing neurological deficit. Autopsy data suggest that there is an overall frequency of detection of AVMs in 4.3 - 6% of population¹. In another autopsy series an incidence of 1.4% was reported, 46 AVMs among 3200 brains; and

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12.2% were symptomatic². In a population-based study in Olmsted County, Minnesota, the detection rate was 1.1 per 100 000 for AVMs when autopsy cases were excluded and 2.1 per 100 000 for all cases. The detection rate for symptomatic cases was 1.2 per 100 000 person-years³. The most common type of vascular malformation detected was AVM, followed by venous malformation and cavernous malformation. Incidence of AVMs is generally considered to be 1/7th to 1/10th of aneurysms.

NATURAL HISTORY AND CLINICAL PRESENTATION OF CEREBRAL AVMS

Prevalence data suggest that up to 0.1 percent of the population (300,000 persons) in the United States may have an arteriovenous malformation⁴. Autopsy data suggest that only 12 percent of arteriovenous malformations are symptomatic during life. More than 50% of AVMs present with spontaneous intracranial hemorrhage⁴. Intracerebral hemorrhage (41-79%) occurs more commonly, although subarachnoid hemorrhage (10-20%) and intraventricular hemorrhage (5-10%) can also occur. Rarely AVMs can present with subdural haematomas due to its location. Severe vasospasm from AVM-related hemorrhage is distinctly uncommon, although it is occasionally noted^{5, 6}. After hemorrhage next most common presentation is seizure,

which occurs in 20% to 25% of cases⁷. Seizures can be either focal or generalized and may be an indicator of the location of the lesion. Other presentations include headaches in 15% of patients, focal neurological deficit in fewer than 5% of cases, pulsatile tinnitus and hydrocephalus due to mass effect. Vascular malformation-related steal phenomena causing focal neurological deficit by altering perfusion in the tissue in the region of the AVM are distinctly uncommon⁸.

The overall frequency of hemorrhage caused by vascular malformations in stroke registries indicates a 1% occurrence of AVM-related hemorrhage among all strokes⁹. The available natural history studies indicate an overall risk of initial hemorrhage of 2% to 3% per year^{7, 8, 9, 10}. Mortality from the first hemorrhage is between 10% and 30%, although some data suggest that the mortality rate may be lower¹¹, and 10% to 20% of survivors have long-term disability^{7,8,12}. In one study¹² a cohort of 281 consecutive, prospectively enrolled patients was investigated to evaluate the risk for hemorrhage. If one assumes an annual hemorrhage risk among people with previously unruptured AVMs of 2% to 4% per year, the lifetime risk of intracranial hemorrhage in a person with an AVM is approximated by the following formula^{13, 14}: 'Lifetime risk (%) = 105- the patient's age in years'.

In a study the risk during the first year after initial hemorrhage was 6% and then dropped to the baseline rate of 2-4% and became similar to symptomatic patient without bleed; whereas in another study⁹, risk of recurrence of bleeding during the first year was 17.9%. Permanent disability is twice of mortality per episode of hemorrhage - 20% to 30%¹⁰. In a prospective study¹², during a short mean follow-up of 8.5 months, the risk of recurrent hemorrhage was 17.8% per year after presentation with hemorrhage. In that study, only 20 patients were still being followed up who were untreated at 1 year after hemorrhage; the risk of recurrent hemorrhage was 32.9% in the first year after hemorrhage and decreased to 11.3% in subsequent years¹². The increased rate in the first year after initial hemorrhage has not been noted consistently¹⁰.

Evidence obtained from imaging studies suggesting that radiological parameters may be predictive of hemorrhage risk. There are data that suggest that prior hemorrhage is a strong predictor of hemorrhage¹¹. The other parameters which help in predicting the higher risk of bleeding are small AVM size in terms of maximal diameter or volume of AVM¹⁵; however it has not been noted consistently¹¹. High feeding artery pressures may also be related to bleeding risk. AVMs in a periventricular or intraventricular location may also be at increased risk¹⁶, although this has not been found in all studies¹⁷.

The possible sites of hemorrhage in AVMs include nidus, proximal arterialized vein, intranidal aneurysm and feeding artery aneurysm. Characteristics of the venous drainage system, including presence of deep venous drainage, have been reported to be a predictor of presentation with hemorrhage¹⁸ or occurrence of hemorrhage during follow-up

in cases initially presenting with or without hemorrhage¹¹. In one retrospective study independent predictors of presentation with hemorrhage included central venous drainage, intranidal aneurysm, and periventricular or intraventricular location¹⁶. In another study, univariate analysis predictors of presentation with hemorrhage included deep venous drainage, arterial supply via perforators, intranidal aneurysms, multiple aneurysms, vertebrobasilar supply, and basal ganglia location. Single draining vein, impaired venous drainage, and deep venous drainage alone were factors in another study¹⁸. Impaired venous drainage was not an important factor in 2 other studies¹⁶, nor was a single draining vein. Presence of a venous varix was also not predictive of hemorrhage¹⁸. The nature of the arterial system may also be important; detection of intranidal or saccular aneurysms appears to be an important finding^{16, 19}. A low-risk group (risk of 1.0% per year) had no history of prior hemorrhage and >1 draining vein in a compact nidus, whereas a highest-risk group (8.9% per year) comprised those who had a prior hemorrhage, a single draining vein, and/or a diffuse nidus. The factors that determine hemorrhage in a case of AVM is given in Table 1.

Table 1: Morphological Features associated with Hemorrhage

1. Central venous drainage or single draining vein
2. Periventricular / Intraventricular / Basal ganglionic location
3. Arterial supply from perforating vessels
Vertebrobasilar system
4. Intranidal aneurysm
5. High intranidal pressure translated to feeding arteries
6. Venous outflow stenosis
7. Smaller sized AVM (<2.5cm)
8. Feeding artery aneurysm – 10-15%
9. Presence of Hypertension

MANAGEMENT OF CEREBRAL AVMS

The goal of treatment is complete obliteration of nidus to get the cure. For management comprehensive evaluation of a patient with an AVM includes a detailed clinical examination and radiological evaluation of the anatomy with MRI scanning and arteriography. After the comprehensive evaluation has been performed, decisions can be made regarding the best management approach by comparing the natural history of the lesion with the intervention-related morbidity and mortality.

PRE-PROCEDURAL IMAGING IN CEREBRAL AVMS

The pre-procedural imaging in Cerebral AVMS relies on Digital Subtraction Angiography (DSA), which is still the gold standard for diagnosis and management. Superselective DSA in various phases, using microcatheter is absolutely essential for delineation of complete angioarchitecture of AVMs (Fig 1 and 2). Arterial phase shows wedge shaped nidus with broad base towards the cortex and apex towards

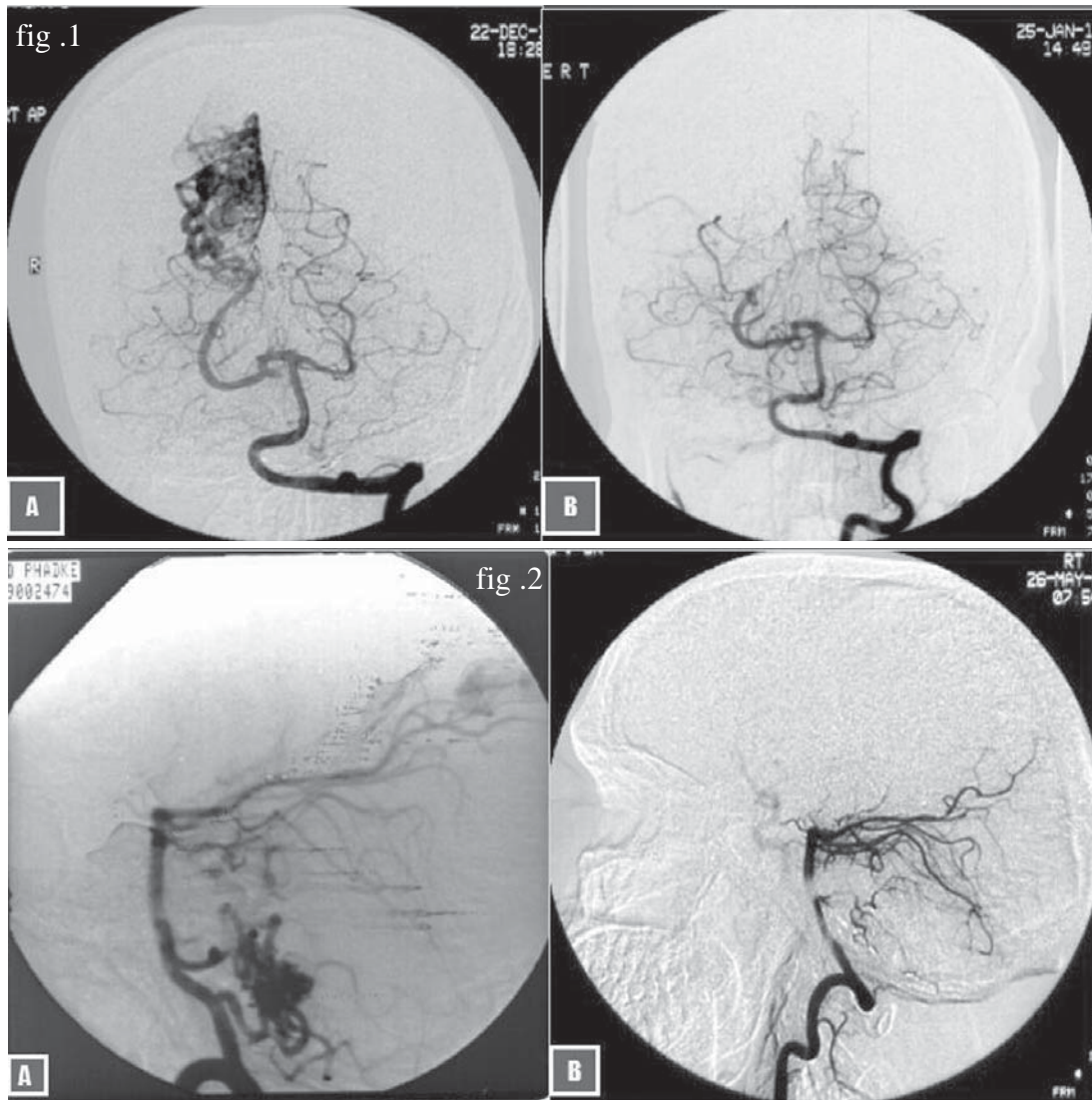


Figure 1 & 2 : Superselective DSA in various phases, using microcatheter is absolutely essential for delineation of complete angioarchitecture of AVMs. Arterial phase shows wedge shaped nidus with broad base towards the cortex and apex towards the ependymal surface. AV shunting is characteristic of AVM but not pathognomonic. Draining veins are dilated and tortuous. Fig. 1A & 2A are pre embolisation; Fig. 1B & 2B are post embolisation angiogram images.

the ependymal surface. AV shunting is characteristic of AVM but not pathognomonic. Draining veins are dilated and tortuous. The delineation of both the superficial & deep venous system is essential as drainage may occur in varying combination. Identification of other risk feature like venous stenosis, venous varix and venous aneurysm is essential. Angioarchitecture must be completely analysed for effective interventional treatment strategy as outlined in Table 2.

CT Scans entails performing both plain and contrast enhanced brain CT. CT demonstrates serpiginous iso or hyperdense tangled mass of vessels which show intense enhancement. There may be evidence of hemorrhage, calcification, gliotic scar and ischemic changes in the surrounding brain. Mass effect is also seen due to large

Table 2 : Comprehensive Angioarchitecture Study

Parameter
1. Number of feeding vessels
2. Territory of feeding vessels
3. Nidus
4. Draining Vein
5. Feeding artery aneurysm
6. Intranidal aneurysm
7. Intranidal fistula
8. Venous stenosis/venous ectasia
9. Presence of large venous sac
10. Number of feeders opening in sump
11. Draining veins arising from venous sac
12. Nidus and fistulas opening orientation at sac

tortuous draining veins and size of nidus. There may be hydrocephalus either due to mass effect or due to venous high pressure. CT angiography may help in demonstrating nidus, feeding artery aneurysm and assessment of nidus volume. CT is also valuable in planning of Stereotactic Radiotherapy.

MRI and MRA are superior to CT in demonstrating the topography of the AVM. MR is more accurate than CT in determining the overall size of the nidus. It is also better suited to demonstrate subacute and chronic hemorrhage and secondary changes in the adjacent brain. The increased signals within the vessels may be due to thrombosis, slow flow or turbulence. MRA may help in identifying dural feeders, size of the nidus, feeder and intranidal aneurysm. Functional MRI using Bold technique are useful to localize the cortical functions which will help in planning of treatment of AVM and also in follow up after treatment particularly after Stereotactic Radiotherapy.

Spetzler and Martin Grading of AVMs²¹ is based on size, location and deep venous drainage. Analysis of size yields scores of 1,2 and 3 for sizes 0 to 3 cm, 3.1 to 6 cm and greater than 6 cm. Non eloquent location are given a score of 0, while eloquent location are given a score of 1. Eloquent Areas comprise sensory motor cortex, language area, visual cortex, hypothalamus, thalamus, internal capsule, brainstem, cerebellar peduncles and deep cerebellar nuclei. Deep venous drainage absence or presence is valued as 0 or 1 respectively. Inoperable AVMs are put in grade VI. One grade is added in presence of acute hemorrhage. A subclassification of A, B, C is added as necessary, to associate three common conditions associated with increase the risk of bleed, with A denoting constriction or stenosis of venous drainage, B indicating presence of incidental feeder or intranidal aneurysm, and C suggesting periventricular location, The treatment options for cerebral AVMs include Surgical excision, Endovascular embolization, Stereotactic radiotherapy or a combination of above. No active intervention is an important option in select cases. The factors to be considered before making a decision to treat the AVMs include a) natural history, b) age of the patient, c) general health and clinical condition, d) identifying elderly patient with cardiac problem where stereotactic radiotherapy may be preferred or no treatment and e) occupation and lifestyle.

EMBOLISATION FOR CEREBRAL AVMS

The current indications for embolisation include a) patient presenting with intracranial hemorrhage or subarachnoid hemorrhage; b) progressive neurological deficit; c) uncontrolled seizure due to AVM; d) young patient with bleed or deficit or seizure; e) presurgical / pre-RT embolization and f) as a palliative measure. Endovascular Treatment may be done as a) definitive therapy in 20 -40% cases (Fig 3); b) preoperative embolization before surgical excision or Stereotactic Radiotherapy to reduce the size of AVM; c) in large AVM located on eloquent areas and fed by branches of all three cerebral vessels; d) feeders not accessible for surgery

–intraventricular, basal ganglionic, thalamic & brainstem; e) deeply located feeders e.g. ACA feeders in parasagittal AVMS, ACA / PCA feeders in posterior frontal and parietal AVMS, PCA feeders in paratrigonal /posterior temporo-occipital AVMS. The optimum time of embolization is generally after an episode of hemorrhage while most authorities recommend a waiting period of 4 to 6 weeks.

The goals of treatment are a) complete obliteration of AVM nidus for complete cure; b) reduction in the size of the nidus before surgery or Stereotactic Radiotherapy; c) obliteration of surgically inaccessible and deep location of AVMS; d) embolisation of feeding arteries from PCA branches, choroidal arteries, anterior/posterior perforating arteries; e) occlusion of Intranidal aneurysm and e) occlusion of high flow fistulas.

The current understanding of hemodynamics of AVM is focused on ‘nidus’, with endovascular embolization aimed at its obliteration. A hemodynamic profile of AVM is a function of number, position & caliber of feeding pedicles, length of feeding pedicles, resistance of the nidus, venous drainage and associated fistulae. Typically flow in an AVM ranges between 150 to 900 ml with an average of 490ml/min. The intraluminal pressure of feeding pedicle in small AVMS is high while large AVMS have low feeding artery pressure. AVM embolization should be done as staged procedure range from 48 hours to 2 wks to 2 months. This selection aims to avoid effects of ‘Normal Perfusion Pressure Breakthrough’ (NPPB) because hemodynamics get normalized in 10 days to 2 weeks time. Typically one to four pedicles per session may be embolised. Feeding artery pressure measurement is important, since pressure in the feeding pedicle has been correlated with risk of hemorrhage. Furthermore, the reliability with microcatheter has been confirmed. Pedicle pressure tends to rise during embolization and approach systemic MAP and greater than 75% MAP in the pedicle may be associated with development of Normal Perfusion Pressure Breakthrough (NPPB). Common complications of glue embolisation include a) hemorrhage which can be *acute* due to vessel perforation or *delayed* due to NPPB or venous occlusion due to glue; b) Stroke which can be attributable to catheter induced thromboembolism or reflux of glue in normal vessels and c) gluing of microcatheter.

Ethanol embolisation uses ethanol which is a very potent but dangerous embolic material²². It causes intense vasospasm and can cause infarcts if reflux in normal vessels. The mechanism of action is denudation of endothelial cells, precipitation of protoplasm, fracturing of blood vessel wall up to the level of internal elastic lamina all leading to intense vasospasm which gradual causes thrombosis of the AVM. The incidence of NPPB with ethanol is less due to gradual thrombosis & occlusion of AVM. Upper safe limit of ethanol is not known but a dose of 0.5ml/kg body weight may be safe. The maximum recommended of Ethanol is up to 1ml/kg body weight.

SURGERY FOR CEREBRAL AVMS

Surgery is generally done as an elective procedure. The

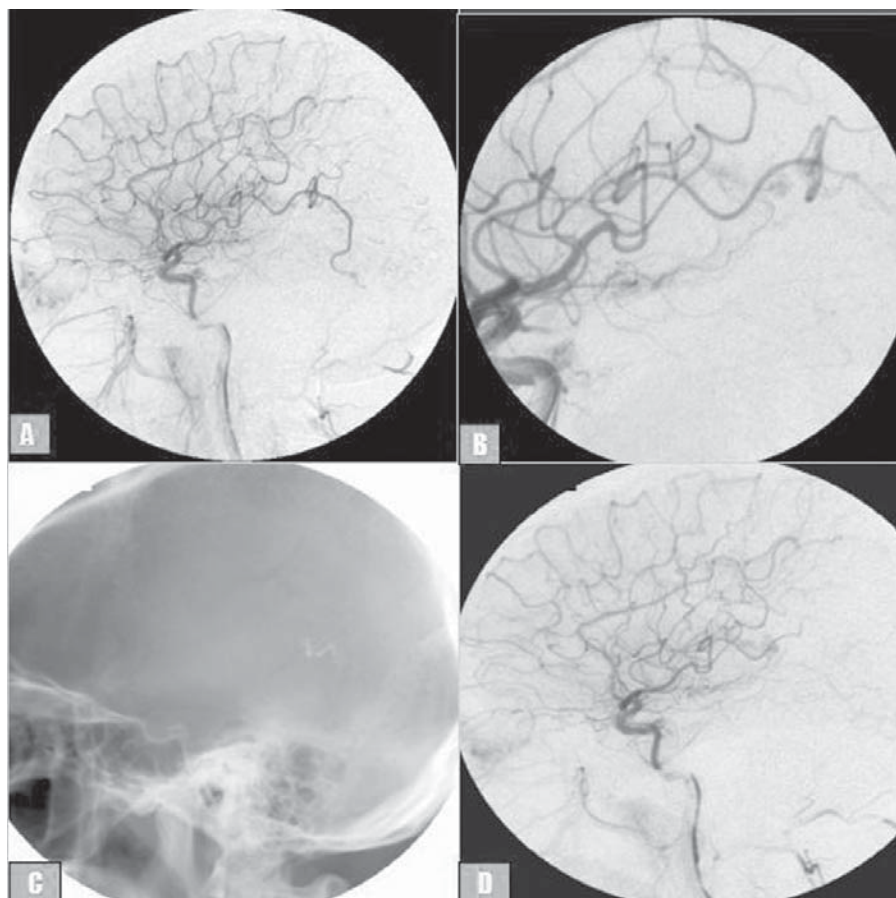


Figure 3 : Endovascular Treatment showing complete obliteration of AVM nidus indicately complete cure; reduction in the size of the nidus; occlusion of Intranidal aneurysm

factors of to be considered for surgical excision of cerebral AVM includes: location, type of lesion, larger sized malformation. Location such as brainstem, posterior limb of internal capsule and deep gray matter nuclei are considered as surgically challenging.

STEREOTACTIC RADIOTHERAPY FOR AVMS

Stereotactic Radiotherapy irradiates blood vessels of the AVM to cause progressive luminal obliteration & thereby preventing hemorrhage. It is currently indicated in following situations : a) most appropriate for small AVMs in eloquent areas, giving satisfactory results with less complications, and b) lesions with volume less than ten cubic centimeter and maximum diameter <3cm. The thrombosis rates in patients undergoing stereotactic radiotherapy by gamma or x-knife²³, is expressed as first and second year occlusion rates. Literature evidence supports the following occlusion rates: 1st and 2nd year occlusion rates of 33.7%-39.5% 79% to 86.5% from Steiner et al, 2nd year occlusion rate at 64% from Yamamoto et al and 80% from Lunsford et al.

Clinical experience reveals that stereotactic radiotherapy in properly selected small AVMs can leads to complete AVM

obliteration in ~80% of patients within 2 years. In MRI, the indicator of successful treatment after stereotactic radiotherapy is denoted by a decreased size of the nidus, a decreased number of flow voids, presence of hyperintense signals on T2 images and a persistent contrast enhancement in the area of nidus. Complications of Stereotactic Radiotherapy for AVMs comprise a) hemorrhage with an incidence of 2% to 3% per year, since there is no protective effect against hemorrhage and b) Radiation induced complications like necrosis that occur after 12 to 18 months. The incidence of Post radiotherapy syndrome may be under estimated, but uncommonly they can exacerbate seizure.

CONCLUSION

The main goal of treatment of cerebral AVM is complete obliteration of the nidus or AVM per se. To achieve this goal a careful judgment influencing the outcome based on various factors should be taken. A multidisciplinary approach is provides the best outcome. It is still not clear whether partial obliteration of the lesion in an attempt to reduce mass effect and steal in patients with progressive neurological deficit or medically uncontrolled seizures is beneficial. Thus management of AVMs is still a challenge for medical professionals.

REFERENCES

1. Michelson WJ. Natural history and pathophysiology of arteriovenous malformations. *Clin Neurosurg.* 1978;26:307-313.
2. The Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. *N Engl J Med.* 1999;340:1812-1818.
3. Brown RD, Wiebers DO, Torner JC, et al. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. *Neurology.* 1996;46:949-952.
4. Brown RD Jr, Wiebers DO, Torner JC, O'Fallon WM. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intracranial vascular malformations in Olmsted County, Minnesota. *J Neurosurg.* 1996;85:29-32.
5. Maeda K, Kurita H, Nakamura T, et al. Occurrence of severe vasospasm following intraventricular hemorrhage from an arteriovenous malformation. *J Neurosurg.* 1997;87:436-438.
6. Kothbauer K, Schroth G, Seiler RW, and Do DD. Severe symptomatic vasospasm after rupture of an arteriovenous malformation. *AJNR Am J Neuroradiol.* 1995;16:1073-1075.
7. Wilkins RH. Natural history of intracranial vascular malformations: a review. *Neurosurgery.* 1985;16:421-430.
8. Mast H, Mohr JP, Osipov A, et al. "Steal" is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. *Stroke.* 1995;26:1215-1220.
9. Fulst D, Kelly DL. Natural history of arteriovenous malformations of the brain: a clinical study. *Neurosurgery.* 1984;15:658-662.
10. Ondra SL, Troupp H, George ED, et al. The natural history of symptomatic arteriovenous malformations of the brain: a 24 year follow-up assessment. *J Neurosurg.* 1990;73:387-391.
11. Hartmann A, Mast H, Mohr JP, et al. Morbidity of intracranial hemorrhage in patients with cerebral Arteriovenous malformation. *Stroke.* 1998;29: 931-934.
12. Mast H, Young WL, Koennecke HC, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. *Lancet.* 1997; 350:1065-1068.
13. Kondziolka D, McLaughlin MR, Kestle JR. Simple risk predictions for arteriovenous malformation hemorrhage. *Neurosurgery.* 1995;37:851-855.
14. Brown RD. Simple risk predictions for arteriovenous malformation hemorrhage. *Neurosurgery.* 2000;46:1024. Letter.
15. Duong DH, Young WL, Vang MC, et al. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. *Stroke.* 1998;29:1167-1176.
16. Drummond JC, Patel PM. Cerebral physiology and the effects of anesthetic agents and techniques. In: Miller R, ed. *Anesthesia.* 5th ed. New York, NY: Churchill Livingstone; 2000:695-734.
17. Turjman F, Massoud TF, Vinuela F, et al. Correlation of the angioarchitectural features of cerebral arteriovenous malformations with clinical presentation of hemorrhage. *Neurosurgery.* 1995;37:856-860; discussion 860-862.
18. Kader A, Young WL, Pile-Spellman J, et al. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. *Neurosurgery.* 1994;34:801-807; discussion 807-808.
19. Pollack BE, Flickinger JC, Lunsford LD, et al. Factors that predict the bleeding risk of cerebral arteriovenous malformations. *Stroke.* 1996;27:1-6.
20. Brown RD, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. *J Neurosurgery.* 1999;73:859-863.
21. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg.* 1986;65:476-483.
22. Yakes WF, Hass DK, Parker SH, et al. Symptomatic vascular malformations: ethanol embolotherapy. *Radiology.* 1989;170:1059-1066.
23. Yamamoto Y, Coffey RJ, Nichols DA, et al. Interim report on the radiosurgical treatment of cerebral arteriovenous malformations: the influence of size, dose, time and technical factors on obliteration rate. *J Neurosurg.* 1995;83:832-837.

DRUG PROFILE

SOLIFENACIN SUCCINATE

Solifenacin succinate is a muscarinic receptor antagonist. Chemically, it is butanedioic acid, compounded with (1S)-(3R)-1-azabicyclo (2.2.2) oct-3-yl,4-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylate (1:1) having an empirical formula (C₂₃H₂₆N₂C₄H₆O₄), and a molecular weight of 480.55. **Mechanism of Action** : Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion.

Pharmacokinetics : After oral administration of solifenacin to healthy volunteers, peak plasma levels (C max) of solifenacin are reached within 3 to 8 hours after administration, absolute bioavailability of solifenacin is approximately 90%

Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin) and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

INDICATIONS^{1,2} :The drugs are indicated for the treatment of overactive bladder with symptoms of urge incontinence.

DOSE The recommended dose is 5 mg daily, may be increased to 10 mg once daily. If required no dose adjustment is necessary for patients with mild hepatic impairment; for severe renal impairment (CLcr<30 mL/min), and serve hepatic derangement a daily dose of greater than 5 mg is not recommended. Safety and effectiveness in children have not yet been established.

CONTRAINDICATIONS: include urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma; hypersensitive severe hepatic impairment; severe renal impairment or moderate hepatic impairment patient on a potent CYP3A4 inhibitor, e.g. ketoconazole.

PRECAUTIONS^{1,2} : Solifenacin should be used with caution in patients with: bladder neck obstruction hiatus hernia/gastroesophageal reflux; autonomic neuropathy.

Patients with Congenital or Acquired QT Prolongation

The maximum effect of solifenacin can be determined after 4 weeks at the earliest.

DRUG INTERACTIONS

Drugs Metabolized by Cytochrome P450, interaction occurs with CYP 3A4 Inhibitors : (e.g. Rifampicin, phenytoin, carbamazepine)

Ketoconazole, Oral Contraceptives, Warfarin, Digoxin, *Anticholinergic Agents*: More pronounced therapeutic effects and undesirable effects. *Metoclopramide and Cisapride*: Reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract.

ADVERSE EFFECTS^{1,2} Dry mouth, constipation, blurred vision (accommodation abnormalities), urinary retention and dry eyes. The overall rate of serious adverse events in the double-blind trials was 2%.