The Role of Embolisation in the Management of Arteriovenous Malformations

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ABSTRACT

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Arteriovenous malformations in the brain are congenital lesions that present with haemorrhages, seizures, headaches and neurological deficits.

The clinical presentation of AVM are haemorrhages, seizures, headaches sometimes in the form of migraines and neurological deficit5 as a result of injury to the surrounding eloquent brain regions.8 In some instances AVMs are asymptomatic. AVMs usually only present themselves in the second or third decade of life and occurs with equal frequency in both men and women.5

The natural history of AVMs are haemorrhages, seizures, neurological deficits, headaches and death.

Endovascular embolisation is often used to treat small AVMs and is minimally invasive. It can be used prior to both surgery and radio-surgery. Embolisation alone cannot obliterate many morphologically different groups of AVMs. It is normally only used to obliterate smaller AVMs with limited number of feeders.

Nevertheless, embolisation has emerged as a part of multi-modality treatment in the overall management in certain parts of the world. The success of any particular approach depends on a multi-disciplinary team comprising of surgeons and interventional specialists.

Keywords: Arteriovenous Malformation, Clinical Features, Imaging, Management, Embolisation.

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Arteriovenous malformations in the brain are congenital lesions that present with haemorrhages, seizures, headaches and neurological deficits. It can be treated with surgery, radio-surgery and endovascular embolisation, which is the main focus of this essay.
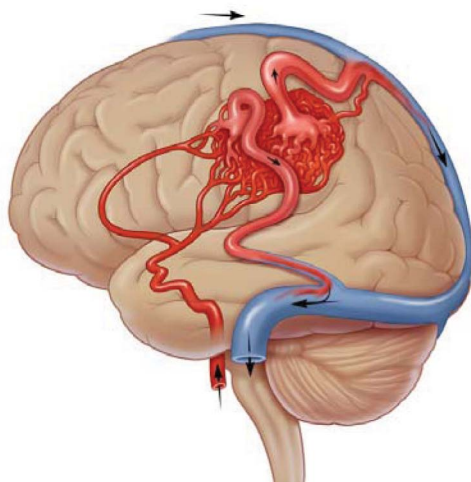
Definition of AVM:

Figure 1. Schematic diagram of an AVM showing the venous conglomerate, the nidus. Taken from: The aneurysm and AVM foundation.

Arteriovenous malformations (AVM) are lesions that result in an abnormal direct connection between arteries and veins, through a venous conglomerate called the nidus.[1] The nidus has no normal capillaries and the AVM is supplied by enlarged arteries and drained by tortuous and dilated veins.[2] As a consequence, blood flow is unregulated and the pressure within the nidus rises, exposing the veins to very high pressures. The abnormal veins have thickened intimae, mural fibrosis
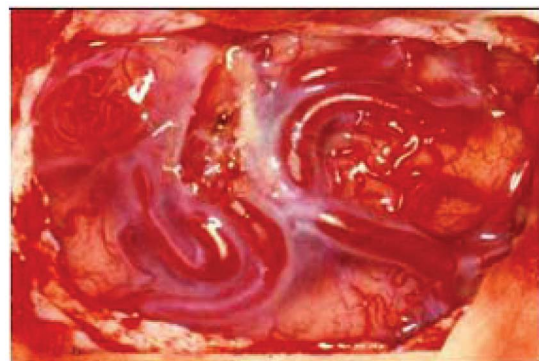

Figure 2. Tortuous and dilated appearance of the draining veins in AVMs Taken from: Universitäts Klinikumbon.

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and narrow lumens with increased amounts of elasticity.[3]

INTRODUCTION

AVMs are considered congenital lesions arising from the unusual connections within the developing arterial and venous plexus that overlies the developing cortical surface in the foetus.[4] The modified vasculature is then incorporated into the brain parenchyma.[5]

The incidence of these congenital lesions varies incredibly but is believed to affect 1.4 per 10,000 individual per year.[5] However, the development of diagnostic imaging procedures has made AVM detection easier. Such imaging procedures include computed topography (CT), magnetic resonance imaging (MRI) that provides information about the exact location of the AVM, angiography that helps in establishing the
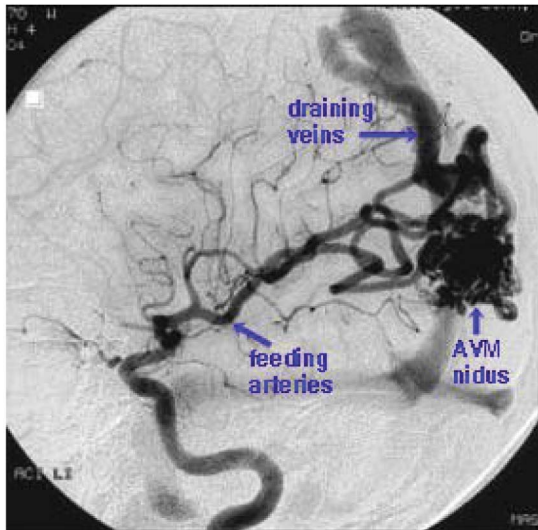

Figure 3. **Temporal lobe AVM on angiogram, which maps out the blood vessels involved and the blood flow through an AVM. Taken from: Universitäts Klinikumbon.**

optimal treatment by mapping out the blood vessels and functional MRI that highlights the AVM's effect on surrounding brain areas.

Arteriovenous malformations were first identified by the ancient Egyptians.[6] Steinhal is credited for giving the first clinical diagnosis[6] while Olivecrona, in 1932, was the first to perform the surgical excision of an aterievenous malformation.[2]

It was after McCormick had published his work (in 1966) titled 'The Pathology of Vascular Malformations,' that vascular abnormalities were classified into sub-groups: cavernous malformation, venous malformation, telangiectasia varix andAVM.[7] This classification helps in the successful management of AVMs.[7]

With respect to this classification, the most common vascular malformation in the under sixteen is AVM.[2]

Presentation

The clinical presentation of AVM are haemorrhages, seizures, headaches sometimes in the form of migraines and neurological deficit[5] as a result of injury to the surrounding eloquent brain regions.[8] In some instances AVMs are asymptomatic.

The major presentation is haemorrhage in approximately half of the patients;[9] in fact the primary reason to treat AVMs is to prevent new or recurrent intracranial haemorrhages.[7] Smaller AVMs have a greater propensity to bleed spontaneously compared to larger malformations.[8] This could be due to more indirect connections and so are exposed to higher flow rates.[8] Despite this, smaller AVMs tend to be asymptomatic in the population since they are less likely to show clinical symptoms of epilepsy or neurological deficit.[6] The second most common symptom is seizure followed by neurological deficit and then headaches.[9]

AVMs usually only present themselves in the second or third decade of life and occurs with equal frequency in both men and women.[5] Children are at a greater risk because they are faced with the period of greatest risk of rupture, which is 15 to 40 years of age.[8] Neonates and infants can present themselves with congestive heart failure as a consequence to AV shunting.[2]

The AVMs reveal themselves in a variety of different signs and symptoms,[9] not all as a result of haemorrhage. Different mechanisms such as venous ischemia, venous outflow congestion, hydrocephalus, disruptions to venous drainage,[9] thrombosis of venous aneurysms[2] and the 'steal phenomenon' can manifest as any of the AVM symptoms.[9] The 'steal phenomenon' is caused by siphoning of blood from adjacent tissue thereby causing ischemia.[8]

However, the angio architecture of the AVM is so intricate that it is difficult to match any one specific mechanism to any one non-hemorrhagic symptom.[9]

Natural History

The natural history of AVMs are haemorrhages, seizures, neurological deficits, headaches and death.[6] The primary risk of haemorrhage as a result of an untreated AVM, is 2-4% per year[11] whilst the primary haemorrhagic risk associated with death is roughly 10% of the above.[8] Despite this, studies have shown that AVM-induced haemorrhages have a lower morbidity

than was originally thought.[10] This could be because the mechanism of AVM haemorrhages are different in different situations;[10] for instance the low-resistance shunts in large AVMs result in lower pressures in the feeding arteries and so confines haemorrhagic size.[10]

Treatment

The aim of treatment is to attain complete and permanent cure with reduced mortality and morbidity.[12] The treatments are surgery, radio-surgery, and endo-vascular embolisation.

Surgery is the gold-standard treatment modality because the excision of AVM eliminates the risk of haemorrhages. However, the main disadvantage is that there is an immediate risk of neurological deficit due to hypo perfusion.[5] Spetzler and Martin proposed a grading system, that helps assess the risks involved in the resection of an AVM. The grades are worked out from a point scoring system according to size, pattern of venous drainage and whether or not in the eloquent regions.[8]

While Grade I malformations are small, superficial and located in non-eloquent regions, Grade V malformations are large, deep and located in eloquent regions and Grade VI is inoperable.[8]

Radio-surgery is used for smaller AVMs and has established itself as a non-invasive treatment.[13] It is often used to treat AVMs in eloquent regions - basal ganglia, thalamus, and brainstem[14] but radio-surgery for large AVMs poses adverse radiation effects.[14] During the latency period of one to three years, the time between radio-surgery and complete obliteration of AVM, there is a risk of haemorrhage.[5] The cause of this acute AVM rupture in the post radio-surgery period differs from that occurring months later.[11] The immediate post radio-surgery rupture is due to an acute inflammatory response associated with radiation, which results in vascular changes eventually leading to this catastrophe.[11] The proper management of haemor-rhagic complications should be based on understanding of each pathological condition;[13] this denotes that each AVM rupture should be treated on an individual basis.

Endovascular embolisation is often used to treat small AVMs and is minimally invasive. It can be used prior to both surgery and radio-surgery,[15] but combining these therapies could mean combing the inherent risks.[16]

Embolisation
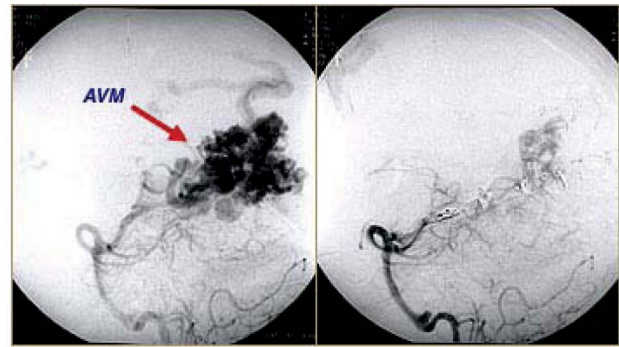
One of the goals of embolisation is to minimize blood

Figure 4. **Occipital lobe AVM (left) and after embolisation (right) After embolisation (right) the vascularity and size of the AVM is reduced. Taken from: University of Pittsburgh.**

loss associated with the resection by reducing the vascularity of the nidus.[17]

The major risks associated with embolisation can be device-related resulting in vessel perforation.[19] Neu-rological deficit such as hemianopia and intracranial haemorrhage can result.[19] The first embolization was in the 1960s and was carried out by Luessenhop.[12] This method involved injecting pellets and saline through a catheter into the cervical internal carotid artery.[12]

Currently embolisation is performed trans- femoral under general anaesthesia.[20] A catheter is then guided into a vessel in the neck; this guiding catheter is flushed with heparinised saline.[20] Then a micro-catheter with a micro guide wire is inserted and is guided as near to the nidus as possible.[20]

Angiograms (Digital Subtraction Angiography) are taken to study the characteristics of the AVM before the procedure. Once the micro catheter is in the area of interest, saline and the embolic agent are injected slowly.[21] This fills up the nidus and refluxes into feeding arteries over a short distance (first penetration).[20]
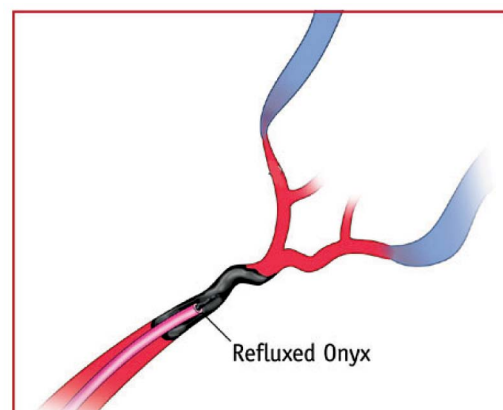

Figure 5. **Refluxed Onyx forms a plug around the micro catheter to prevent it from refluxing into eloquent regions on second penetration. Taken from: Neurosurgery Online.**

The embolic agent actually forms a plug around the tip of the micro-catheter to prevent further refluxing into eloquent brain regions during further injections to the nidus (second penetration).[20]

This injection process is stopped for as long as one minute and subsequent injection are given of smaller volumes.[20] Other reports recommend stopping the injection procedure for two minutes and limiting to smaller volumes.[21]

The embolisation procedure is stopped when the required level of embolisation is attainted, or when forward flow of the embolic agent is restricted and when the maximum safe distance for reflux is reached. During this process, embolisation of the veins or eloquent regions must be avoided.[20] Venous embolisation can be identified by lamination of the vessel
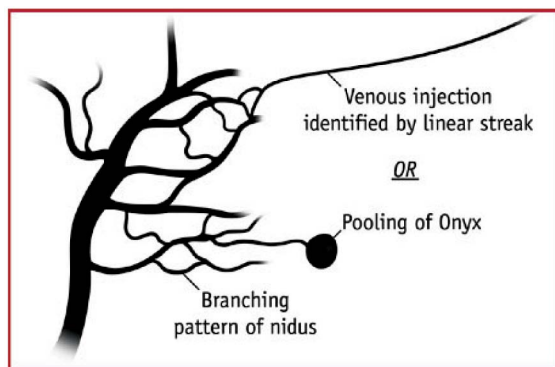

Figure 6. **The accumulation of Onyx and the liner streak- line pattern are ways in which venous injections are identified. Venous embolisation must be immediately stopped Taken from: Neurosurgery Online.**

walls, accumulation of the embolic agent itself and a streak-line pattern that does not exhibit branching on angiograms.[20]

If venous embolisation does occur injection is immediately terminated.[21]

Embolic agents themselves have advanced but its usage depends on the goal of that particular embolization session.[15] The embolic agent of choice used to be n-butyl-cyanoacrylate glue, but due to the difficulty in injecting these particles in high concentrations to reach distal AVM areas and due to its propensity to recanalization, Onyx is fast becoming a replacement.[21]

Onyx is an ethylene-vinyl alcohol copolymer that is dissolved in an organic solvent, dimethyl- sulfoxide.[19] It is advantageous as it allows greater control in injection and thus larger areas of the AVM can be occluded.[21] Before embolisation, tantalum powder is added to the embolic agent to provide radiopacity.[19] Since Onyx is

non-adhesive it provides another advantage in that it reduces the risk of gluing the catheter;[17] it does not fragment on injection as well.[19] High rates of complete or near- complete occlusion can be achieved by several embolisation courses that are associated with little morbidity and mortality.[21]

The slow injection of Onyx is essential for its success, with a volume reduction of more than 90%.[19]

Embolisation as a Multi-modality Treatment

Embolisation can be combined with other procedures depending on the treatment strategy for each individual patient.[17] It can be used prior to surgery and radiosurgery; for embolising related aneurysms, as embolisation alone with the intent to cure or palliation of symptoms.[17]

Embolisation preceding surgery has established itself as a treatment for AVM. The aim is to reduce blood flow making microsurgical resection easier and safer.[12] This procedure aborts feeders, eliminates arterial supply to the nidus as well as eliminating associated intranidal aneurysms.[12] Pre-operative embolisation is also considered useful in large or deeply located AVMs.[22] A series of embolisation sessions help surrounding brain parenchyma adapt to haemodynamic changes, thus reducing postoperative haemorrhages.[12] However, the positive and negative aspects of pre-operative embolisation can influence subsequent surgical intervention.[10] A low number of neurological deficits have been cited in the literature when surgery followed embolisation. In a study of 119 patients six showed disabling deficits of which 3% were the result of surgery and 2% the result of embolisation.[22] There seems to be an advantage for pre-surgical embolisation in contrast to surgery alone which has a higher rate of neurological complications. A total of 50 patients out of the 119 (42%), showed new non-disabling neurological deficit; 32% of these neurological deficits resulted from surgery and 6% from embolisation.[22]

This suggests that it is surgery that increases morbidity rather that embolisation itself. This study utilised only two of the Spetzler-Martin factors-'venous drainage' and 'eloquent regions'- as predictors of surgical risk for neurological deficits. Since neurological deficit followed surgery, it validated the integrity of the grading system.[22] However, it is difficult to assess the role of preoperative embolisation as a treatment, since all patients also underwent surgery.[22]

In another study, with 101 patients, who had pre-surgical embolisation, 97 patients had the AVM success-

fully removed by surgery.[23] Of this 50 patients attained between 50-75% pre-surgical obliteration, and 31 cases achieved between 75-90% obliteration by embolisation.[23] This suggests that pre-surgical embolisation aids in surgical ablation.

Literature suggests that treating Spetzler Martin IV and V AVMs requires a combination of embolisation and radio-surgery.[14] Despite this, there is much evidence that obliteration rates actually decrease when embolisation precedes radio-surgery when compared to radio-surgery alone.[14,24] 61 patients out of 244 were embolised before radio- surgery itself and 47 of these patients were matched according to volume, location and marginal dose with another group of 47 patients that only underwent radio-surgery.[24] Obliteration of the nidus was achieved in 47% multi-modality treatment group, while there was a 70% obliteration success rate for the radio-surgery group.[24] The risk associated with radio-surgery is not eliminated by decreasing AVM volume by embolisation.[24] However, staged gamma knife radio-surgery (a procedure when multiple gamma knife treatments are conducted over a short time period, with each subsequent treatment involving higher doses) is successful in treating large AVMs in eloquent regions independent of whether embolisation precedes radio-surgery or not.[14] The rate of obliteration in staged gamma- knife surgery was 73.7% (14 out of 19 patients) while the obliteration rate with pre-embolisation was 66.7 % (4 out of 6 patients).[14] Though these values show successful obliteration rate, it is evident that preceding embolisation is not advantageous.

However, success has also been reported with preceding embolisation.[25] In a study of 125 patients, 65% attained total occlusion after having partial embolisation. The hemorrhagic risk associated with the residual nidus was comparable to the natural history of the AVM.[25] This contradicting data associated with AVM is suggestive of its ever varying characteristics. However, it is difficult to decide the effects of full embolisation and partial embolisation on the following treatment due to the paucity of details in published papers.

Embolisation Alone

The aim of embolisation is to permanently obliterate the AVM nidus, and restore normal arterial blood flow whilst re-establishing venous drainage.[26] Literature suggests that the success rate of curative embolisation varies greatly from 40% to as low as between 2 and 5%.[26] This could be due to the varying characteristics and the associated aspects related to AVMs. However, obliteration of an AVM by embolisation can be followed by its recurrence.[26] The variation in success rates could be attributed to the development of the collateral supply and the time needed for its development.[26]

The factors affecting success of this procedure relates to the angio-architectural features -size and the number of feeders- of AVM.[16] Valavanis and Yasar gil, in 1988, proposed the topographic classification, which aids in the success of embolic occlusion.[16] According to this classification, AVMs are classified into two main categories- convexial AVMs and central AVMs and each are then divided into supra- and infratentorial subgroups.[27] This classification aids in arriving at a decision to obliterate by embolisation, but is deficient in categorising the type of feeding arteries with AVM locations.[27] Embolisation is more successful in small AVMs, which are 3 centimeters in diameter and have a limited number of feeding arteries.[12] It is also stated that large AVMs can be treated solely by embolisation, when it presents with specific symptoms such as seizures and neurological deficits.[12] Gradual but complete embolisation reduces the blood flow to already hypoperfused and de-autoregulated areas and thereby reduces the risk of haemorrhages associated with Normal-Perfusion Pressure Break- through Syndrome (NPPBS)[17] NPPBS occurs in blood vessels that have lost auto regulatory functions, when blood was diverted away from them into high flow AVMs. When these AVMs are resected or embolised abruptly, blood starts to flow through the vessels once again. Since they have lost auto-regulatory functions, there is a risk of hyper- perfusion and haemorrhage even in the context of a 'normal' arterial systolic pressure.[17] Another advantage of embolisation is that it can treat AVMs that are supplied by the external carotid, which are often associated with headaches.[12] However, the major disadvantage with embolisation is that partially embolised AVMs have a higher rate of haemorrhages compared to untreated AVMs.[12] This is because partial embolization can recruit more feeders over time.[12]

Studies have shown that the embolic agent cyanoacrylate is also a successful agent when it comes to complete obliteration of the nidus. In this study 27 patients out of 42 underwent embolisation with cyanocrylate. Of this 27, curative embolisation was carried out in 10 patients, which had limited feeders of three and the nidus did not exceed 3 centimeters and was accessible by the catheter tip.[26] 6 patients achieved complete embolisation and the follow-ups also showed complete obliteration of the nidus.[26] Therefore 60% of patients (6 out of 10) remained asymptomatic for five to seven

years after embolisation.[26] However, a study with a larger number of patients, claimed that 28 patients out of 101 achieved total occlusion by Onyx.[21] Near- total occlusion was obtained in another 18 patients. Nevertheless, the final number could be an underestimation, since the remaining patients still needs to undergo further embolisation sessions.[21] Morbidity rate of 8% and mortality rate of 3% were calculated, which were impressive for curative embolisation.[21]

This study did not limit itself by specifying certain angio-architectural characteristics for embolisation but it included all types of AVM, thus providing an all inclusive result.

Should AVMs even be treated?

The behaviour of AVMs is difficult to predict, as so many factors play a role in its manifestations.[28] Literature does suggest that non-intervention should be regarded as a form of AVM treatment.[29] Neurovascular teams face the dilemma of balancing the risk of intervention against the natural history of an enraptured AVM.[28] This concept should be based on the risk of the morbidity and mortality of treatment. Obviously this should be less than the death rate from its natural history.[30] Death from natural course of unruptured AVMs is low compared to the 10% morbidity rate associated with any type of interventional treatment.[31] With the development of modern techniques brain AVMs are more commonly diagnosed than previously.[31] This helps to raise awareness of AVMs in the general public and to health administrators which would help in allocating scarce resources appropriately to help in the management of AVM symptoms. The downside of this is that from a commercial point of view, the ever increasing cost of health care insurance is bound to rise further.

The Randomised trial of Unruptured Brain Arteriovenous Malformations (ARUBA) is a multi- centred study that compares treatment strategies (embolisation, surgery, radio-surgery or any in combination) against the conclusion of the natural history of the AVM.[28] This study will not only define the standards against which all other treatments must be compared but also will provide useful information about the technical aspects of embolization.[28]

Does embolisation have a role?

To justify any treatment, there needs to be a high success rate and low complication rate. Therefore, the goal of AVM treatment is to achieve permanent cure and thus eliminate the occurrence of haemorrhages. The

behaviour of AVMs are unpredictable, as many factors play a role in its natural history and post-treatment behaviour.[28] Since the triumph of Onyx, many centers have adopted embolisation as a curative procedure rather than as part of a multi-modality treatment.[32] However, it is difficult to assess the success rate of embolisation as part of a multi-modality treatment since there is no definite end point to discontinue embolisation and attempt other treatment modalities.[33] It is also difficult to understand whether the cause of mortality and morbidity is due to embolisation per se or as a result of the following surgical or radio-surgical procedure.[33]

Nevertheless, it is difficult to assess the role of embolisation, since there is a lack of published data on curative rates of embolisation compared to that of surgery and radio- surgery.[32] However, embolisation plays a role in treating small AVMs, which are less than 3 centimeters in diameter.[32] The results show that embolisation is more successful compared to surgery and radio-surgery alone.[33]

In this age of knowledge, patients have the empowerment to acquire information about procedures and make choices. As a result, they are more inclined to choose minimally invasive procedures with less adverse effects.[33] Therefore, embolisation appeals to patients. It is important to weigh up the benefits and risks of any particular treatment, as insurance companies may as well be an interested party.[28] In budgeting health resources, it is more likely that funds are allocated to already established procedures, so therefore it is important to determine the role of embolisation.

DISCUSSION

Embolisation alone cannot obliterate many morphologically different groups of AVMs. It is normally only used to obliterate smaller AVMs with limited number of feeders. The most worrying aspect of partial embolisation is that it recruits more feeders over time. This contradicts the concept of treatment itself since it seems to suggest that treatment has a greater risk compared to that of the disease running its course. It is important to appreciate the nuances of partial and complete embolisation; for instance gradual but complete embolisation reduces haemorrhagic risk associated with Normal Perfusion Break-through Pressure whilst abrupt embolisation increases the risk of hyper-perfusion and hameorrhages[17]

Nevertheless, embolisation has emerged as a part of multi-modality treatment in the overall management in certain parts of the world. The success of any

particular approach depends on a multi-disciplinary team comprising of surgeons and interventional specialists.

In spite of the increasing safety and effectiveness of embolisation procedures, there is not enough experience to recommend this as a stand alone treatment. The data mentioned above for curative embolisation, though promising, does not include a large enough population and fails to give an unequivocal answer. The results may improve over time with more experience, improvement in technology and understanding of the pathophysiology of AVMs. So there maybe a scope for better results in the future.

CONCLUSION

Embolisation has advantages as part of a multimodality treatment especially when combined with surgery but its combination with radio-surgery is debateable. Embolisation as a sole modality obliterates only certain types of AVMs. However, its curative nature is promising. Therefore, embolisation emerges as a powerful tool in the management of AVMs.

END NOTE

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