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Outcome of Endovascular Treatment of Cerebral Arteriovenous Malformations with Ethylene Vinyl Alcohol Coploymer

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ABSTRACT

Background: Cerebral AVMs are very rare lesions, and this rarity contributes to the difficulty of treating them. There is no consensus concerning the method of treatment to be chosen among neurosurgery, radiosurgery or embolization.

Onyx embolization could serve as a curative option with accepted morbidity and mortality. The introduction of Onyx and of catheters with detachable tips has no doubt increased the rate of endovascular occlusion, and decreased the risks associated with treatment in our experience.

Objective: The aim of the study was to assess the outcome of the use of Onyx in the treatment of intracranial AVMs as curative embolization or before neuro- or radiosurgery

Patients and Methods: This analytical prospective study was conducted on 25 patients who were diagnosed with cerebral arteriovenous malformations and underwent endovascular embolization with EVOH copolymer with curative intent during the study period. Interventional procedures were done in the neuro –endovascular unit, neurosurgery department Ain Shams University Hospitals and associate neuroendovascular unit in El Matarya Teaching Hospital in the period between September 2014 and April 2017.

Results: Actually comparing these results especially concerning the cure rate along with other studies was somewhat confusing and problematic owing to the diversity in results between studies across the last 15 years.

Conclusion: For the cases that are not fulfilling these criteria, embolization should be offered as preparing step for other modality of treatment. In our experience, for curative embolization, the AVM should be small sized (< 3 cm), supplied by one vascular territory, with feeders that can tolerate reflux up to 2–3 cm, with clear proximal parts of the draining veins, and not located in deep structures.

Keywords: arteriovenous malformations - dimethyl-sulfoxide**.**

INTRODUCTION

Despite advances in neurosurgical and endovascular techniques, treatment of intracranial arteriovenous malformations (AVMs) remains challenging, often requiring a multidisciplinary approach. Nidus reduction before surgery or radiosurgery, curative embolization, and palliative embolization of AVMs are the different goals of endovascular treatment [(1)]**.**

Since the first report in the early1960s about transcatheter embolization of cerebral AVMs, a considerable evolution of microcatheter tools, embolization materials, and techniques has improved the success of embolization. Onyx (ev3, Irvine, California) was introduced a few years ago as a new embolic material for the endovascular treatment of brain AVMs. It consists of an ethyl-vinyl alcohol (EVOH) copolymer dissolved in dimethyl-sulfoxide (DMSO) with tantalum powder added for radio-opacity [(2)]**.**

Its slow solidification allows for a more prolonged and controlled injection which permits theoretically slower filling, better penetration, and obliteration of the nidus. The introduction of Onyx into our AVM embolization practice has brought a different endovascular treatment philosophy in which a "cure" is intended in all brain AVMs, rather than this being a presurgical procedure.

The aim of the embolization became, primarily, to cure all small- to medium-sized AVMs by embolization alone, and secondly, to reduce the size of the larger AVMs [(2)]**.**

AIM OF THE WORK

The overall aim of the study was to assess the outcome of the use of Onyx in the treatment of intracranial AVMs as curative embolization or before neuro- or radiosurgery

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as follows: Evaluation of the rates of initial obliteration of AVMs as well as the reperfusion rates after embolization. Assessment of the safety and efficacy of endovascular use of onyx focusing on the embolization techniques. Analysis of the morphologic features of AVMs in which the injection of Onyx is successful and in which the technique fails.

Patients and Methods

This analytical prospective study was conducted on 25 patients who were diagnosed with cerebral arteriovenous malformations and underwent endovascular embolization with EVOH copolymer with curative intent during the study period. Interventional procedures were done in the neuro –endovascular unit, neurosurgery department Ain Shams University Hospitals and associate neuroendovascular unit in El Matarya Teaching Hospital in the period between September 2014 and April 2017.

Patient eligibility: Selection of patients enrolled for the study has been based according to the following criteria:

Inclusion criteria: Patients older than 5 years of age and less than 80 years. Small AVMs ≤ 3 cm or Spetzler-Martin grade 1 or 2 endovascular therapy has been offered as a first-line treatment with the aim of complete obliteration of AVM. Cerebral AVMs Spetzler-Martin grades 3, 4, or 5 underwent multistage approach to AVM embolization or have been emboli zed to achieve size reduction, to enhance the safety of surgery or as palliative treatment. Patients with ruptured AVM referred in the acute stage of their bleeding, the timing of the embolization has been determined based on the angiographic findings. Patients accepting endovascular embolization as the sole treatment modality and refusing other modalities. Patient is not fit for surgery.

Exclusion criteria: AVM that is so small that the pedicle could hardly be recognized that is, the catheterization of the feeding pedicle was anticipated to be risky. AVM is in the brainstem or in a deep location where it is fed by the anterior choroidal artery or deep perforators, so that the reflux might result in neurological deficit. The feeding vessels of the AVM are originating as “en-passage” vessels, and there is not a sufficient segment for Onyx reflux. Patient presented with hemorrhage and has a hematoma that necessitates surgical evacuation, surgery has been done first. Cases treated by radiosurgery or surgery as the initial treatment, except in the patients who had surgical hematoma evacuation only. Patients with vein of Galen malformations, pial or dural arteriovenous fistulas, facial AVMs, or spinal AVMs have been excluded. Old age with poor medical condition that can't withstand multiple sessions.

Ethical considerations: The study was approved by Ain Shams University Faculty of Medicine Ethical Committee.

Treatment decision and plan was carried out in a multidisciplinary approach consisting of neuroendovascular surgeons, vascular neurosurgeons and neurosurgeons with experience in radiosurgery for assessment of all therapeutic options.

Assessment of the patient and designing a plan to accomplish the goals of treatment was done after a good understanding of: the pretreatment angiographic studies, clinical picture and apparent influence of the angioarchitecture on the natural history of each individual arteriovenous malformation. A preliminary assessment of the technical possibilities and difficulties was done.

Patients were then offered different modalities of management including expectant management with formulation of the reasonable risks, expectations and results were done for each therapeutic plan.

All patients accepting endovascular embolization as a modality of treatment and their families have been informed of the risks and benefits of the intended procedure by the treating neuroendovascular surgeon. A written consent form is signed at least 24 hours before endovascular intervention.

Data collection: All patients enrolled in the study underwent preprocedural, procedural and postprocedural assessments.

RESULTS

Table (1): Age groups of the studied patients

Age(years)	Number of patients	Proportion (%)
10-20	5	20%
20-30	10	40%
31-40	5	20%
41-50	3	12%
>50	2	8%

Table (2): Presentation distribution in cerebral AVM patient

Presentation	ICH	Seizure	Headache	Neurological deficit
Number	16	4	3	2
Proportion %	64%	16%	12%	8%

Table (3): Preinterventional modified Rankin score (mRS) distribution.

mRS	0	1	2	3	4	5	6
Number	9	8	4	3	1	-	-
proportion%	36	32	16	12	4	-	-

Table (4): Topographic distribution of cerebral AVMs.

AVM Location	Frequency	Proportion%
Frontal	10	40
Parietal	2	8
Occipital	5	20
Frontoparietal	2	8
Frontotemporal	1	4
Occipitoparietal	2	8
Cerebellar	3	12

Table (5): AVM distribution as regard, eloquence and venous drainage.

	Number	proportion %
Size		
Small	17	68 %
Medium	8	32 %
Large	-	-
Eloquence		
No	20	80%
Yes	5	20%
Venous drainage		
Superficial	19	76%
Deep	1	4%
Both	5	20%
Number of draining veins		
single	11	44%
multiple	14	66%

Table (6): showing AVM grading as regard SMG and Buffalo score

	Number	Proportion %
Spetzler-Martin Grade		
I-II	17	76%
III	5	20%
IV-V	1	4%
Buffalo Score		
1	9	36%
2	7	28%
3	7	28%
4	2	8%
5	-	-

Table (7): Angiogrphic features of AVM

		Frequency (N)	PROPORTION(%)
Arterial feeder territory			
	MCA	12	34.2%
	ACA	10	28.5%
	PCA	7	20%
	SCA	3	8%
	MA	3	2.8%
Number of feeding arteries	(>3) arterial feeders	11	44%
	(≤3) arterial feeders	14	56%
Diameter of arterial pedicle	Majority (diameter >1 mm)	16	64%
	Majority(diameter ≤1 mm)	9	36%
Nidal configuration	compact	21	82%
	diffuse	4	16%
Associated aneurysms		3	12%
fistulous comonent			
	pure fistulous		
	mixed plexiform and fistulous component		

Table (8): Angiographic outcome of onyx embolization

Nidal occlusion	Frequency	Proportion %
Complete	17	68%
Partial	8	32%

Table (1): Clinical outcome measured by mRS compared per and postprocedural

	Preprocedural	Early postprocedural	Late postprocedural	P value
mRS (average ±SD)	1.04±1.02	1.75±1.2	1.55± 1.1	0.152

DISCUSSION

The ultimate goal of treatment of brain arteriovenous malformation (AVMs) is to reduce the risk of bleeding by complete obliteration of the vascular nidus. This has traditionally been achieved by surgical resection; however, the developments of new embolic materials like Onyx and improvements in stereotactic radiosurgery have introduced new treatment options for these lesions.

And despite this brain AVM continue to pose a special challenge to the treating physician and treatment is highly dependent on the experience of the institution. The current work critically examined our ongoing experience in the endovascular treatment of brain AVM using onyx, in an attempt to identify potential strengths and pitfalls of this technique.

During the last years since the introduction of Onyx and advancement in microcatheters especially the introduction of detachable tip microcatheters, the treatment of brain AVM has undergone a conceptual change in our practice. Endovascular treatment has become our main treatment modality for these lesions, with surgery and radiosurgery reserved as adjuvant treatments when required. This change has brought about several issues concerning both the success and complication rates of treatment

Our study was conducted on 25 patients diagnosed to have cerebral AVMs whom demographic distribution was consistent with the previous studies reflecting the common epidemiological distribution that the disease exhibit. In our study the male:female ratio was 1.27 and this was similar to that be demonstrated in the studies of ***Hofmeister et al.*** [4] ***ApSimon et al.*** [5]**.**

Although the study ***of Lopes et al***. [6] concerning gender distribution has revealed more female predilection with a female: male ratio 1.1:1, this difference in sex predilection had no impact on the final results but in a part reflecting the sporadic nature of cerebral AVMs with no obvious pattern of genetic predisposition and inheritance. This was also supported by the fact that none of the cases enrolled in our study has family history or associated vascular malformations. The same finding was found in the study of Limaye ***et al.*** [7]. This conclusion added more evidence to the sporadic nature of cerebral AVMs. None of the female patients in the study were pregnant at time of presentation or intervention. The concept that pregnancy may increase the risk of bleeding is somewhat overestimated as shown in the study of ***Liu et al.*** [8] who found no increased risk of hemorrhage during pregnancy.

The mean age of patients was **27.7±9.5** with more than **60%** of patients **<30** years and this age distribution was similar to what be demonstrated ***by Petridis et al***. [9], ***Lopes et al.*** [6]**.** The proportion of patients **> 50** years was **8%** may be partially explained by diagnostic bias, i.e. hemorrhagic strokes in the elderly do not always result in angiographic (including CTA or MRA) examination, and some AVM hemorrhages in this age group are probably misjudged as spontaneous intracerebral hemorrhages**.**

Heamorrage was the most common presenting symptom among patients enrolled in our study occurring in **64%** which was the same condition observed in the study of ***Crawford et al.*** [10], ***Lopes et al***. [6] followed by seizures in **16%**, headache **12%** and focal deficits in **8%**.

In a study conducted by ***Pikus et al.*** [11] **63%** of the AVM patients presented with hemorrhage with or without seizure, **18%** with seizure alone,.

In another study conducted by ***Hillman*** [12], it was found that the rate of hemorrhage in AVM patients was **69.6%,** while that of seizures was **14.8%. 5.9%** of the patients presented with progressive neurological deficits and **3.7%** with headache. **4.4%.**

On the other hand, more recent patient's series as in in this Meta analysis, involving 2086 patients, conducted by ***Zhao et al***. [13] reported a frequency of 43% for the hemorrhagic presentation of AVMs. Headache was the second common clinical presentation and constituted 25%. Seizures occurred in 17% while neurological deficits occurred in 9%. This actually reflects the fact that the increasing availability of neuroimaging is gradually changing the pattern of symptomatology of AVM presentation

towards diagnosis in the absence of hemorrhage. Nonetheless, hemorrhagic stroke due to AVM rupture has remained the single most common presenting symptom confirming the associated epidemiological importance of cerebral AVMs due to related mortality and morbidity and all studies concerning AVMs are always will be closely related to prediction of risk of bleeding and prevention of rebreeding.

Procedural data :

All procedures in this study were performed by the same neuroendovascular neurosurgeon that was highly qualified and experienced in this field.

All procedures were performed using coaxial system depending on guiding catheter and DMSO compatible microcatheter with no complications related to identify and navigate target arterial pedicles with the advantage of reduced time of the access phase and not adding complexity to the procedure this is supported by the fact that most patients are of young or middle age with healthy and straight vessels. This was consistent with experience in onyx embolization stated by ***Strauss et al.*** [14], ***Saatci et al.*** [2].

Number of embolized pedicles per session was ranging from 1-3 per session with the majority of procedures(80%) involve embolization accessing single pedicle with high rate of nidal obliteration more than apparently anticipated on selective angiography performed pre-embolization. The number of accessed pedicles used for embolization is not dependent on the number of arterial feeders. Instead this depends largely on the cohesive nature of Onyx which flows like lava penetrating from one compartment to another compartment rendering apparently mulicompartmnetal AVM into monocompartement one with potentially retrograde filling of the other feeding vessels. Therefore effective nidus obliteration may be achieved from 1 or 2 convenient pedicles without taking the risk of several pedicle microcatheterizations as well as injecting from more risky pedicles such as those that are too tortuous, too distal, too thin, or those supplying normal parenchyma or eloquent areas.

This was consistent with technical findings published by ***Strauss et al.*** [14], ***Maimon et al.*** [15], who concluded that" when evaluating an AVM for embolization with Onyx, one has to consider the aspects unique to embolization with Onyx, namely injection of relatively large amount of Onyx through a single feeder and opening of intra nidal channels between different compartments". They also stated that Complications tend to increase with increase the number of arterial pedicles accessed per session.

The volume injected of onyx per session was ranging from 0.7-4.5 ml with mean 2.3 ±1.4 ml with no complication appear to be attributed to this amount. There was significant relation (p value <.005) between the amount of onyx injected and rate of obliteration. However the protocol of onyx embolization in our institute implies to limit the amount of Onyx injected in a single session to 4–5 cc and divide the treatment to multiple sessions as needed. This was derived from our early experience of onyx embolization which also was consistent with ***Strauss et al.*** [14] Who showed that the amount of onyx injected per session was significantly higher in the complication group (5.7±3.1 cc vs. 2.8±2.4 cc, P<0.05).

The mean time spent during onyx embolization was 23.2 ±5.8 min/session ranging from 17 to 32 min. with no complication related to retrieval of microcatheter from onyx cast. This was in large part due to the cohesive nature of Onyx (compared with the adhesive nature of N-butyl cyanoacrylate (n-BCA)), which avoids adherence of the embolic material to the microcatheter tip and thus enables longer working times and, consequently, a more controlled and complete embolization and also there was sufficient time for angiographic checks during the prolonged injections. According to ***Saatci et al.*** [3]***; Strauss et al.*** [14]: While endovascular embolization of AVMs traditionally has been an adjuvant treatment, or used in the context of multimodal therapy, it is increasingly possible to achieve complete radiographic AVM obliteration through embolization procedures.

All procedures used DMSO compatible microcatheters which have a relatively thick wall in order to handle the high pressure inside the lumen during the injection of Onyx. This made them stiffer and less supple requiring a guide wire for navigation,

and therefore difficult and dangerous for use in small tortuous vessels with theoretically increased risk of vessel perforation especially when compared to those used with cyanoacrylates.

In our study, we did not encounter such complication. This can be attributed to highly skilled operator who use "J" shaped guide wire in front of the microcatheter during navigation to reduce the risk of vessel wall puncture. Another key factor is the good selection of the artery accessed for embolization whose size can accommodate the stiff onyx compatible catheters.

In our opinion, this high cure rate in our study could be simply explained by the prior intention to completely occlude the lesion whenever possible, the use of Oynx especially if combined with detachable tip catheters which permit longer injection time, and the use of staged approach and lastly which is most important case selection.

AVM angioarchitecture- radiographic outcome correlation:

In fact high cure rate depends mainly on selection of suitable cases to achieve curative endovascular embolization without major complication. In our study we tried to test different angioarchitectural features in correlation with obliteration rate comparing between patients who achieved angiographic cure and patients who had partial occlusion. This was limited by the small sample size and the limited follow up period.

We found only size of AVM nidus and non –eloquent location was significantly correlated with increasing obliteration rate. While other features fail to establish a statistically significant relation with cure rate. Small size of AVMs (<3 cm) were significantly associated with higher obliteration rate and cure rate. Also non eloquence of AVM location was significantly associated with higher cure rate. This was also concluded by ***Saatci et al.*** [3] and ***Lopes et al.*** [6], ***Strauss et al.*** [14].

To be fair, the relation between the AVM size and eloquency of nidus location and AVM treatment outcome was originally established by spetzler -martin grading since 1986 and its recent modifications which provide a means of risk stratification for the microsurgical management of AVMs. Such a logic relation continue to impose itself forcefully and can be easily applied in endovascular embolization of AVM since the smaller the size of the nidus the shorter the procedure and the less volume of embolic material required for obliteration and vice versa. These factors may decrease the chance of complication or abortion of the procedure.

While in searching for risk-stratification tool for endovascular treatment of AVMs, Eloquence of location was incorporated in both Feliciano grading system suggested by ***Feliciano et al. 2014***[16] and in Buffalo score suggested by ***Dumont et al.2015*** [17] while AVM size was incorporated in AVMES score proposed by ***Lopes et al.*** [6] with stratification similar to that of S-M grading. ***Lopes et al.*** [6] has introduced the concept of 'vascular eloquence' which is unique to the AVMES. An arteriovenous malformation (AVM) was deemed eloquent if the arterial pedicle was<20 mm from the internal carotid artery or the first segment of *cerebral* arteries (eg, A1, M1, P1 segments) or too small for microcatheterization.The assignment of non-eloquence was given if an AVM did not meet eloquent criteria.

When performing endovascular embolization, ***Lopes et al.*** [6] noted that 'vascular eloquence' to be of greater importance than traditionally *described brain eloquence* since a proximal, parent vessel occlusion would result in significant, often hemispheric, deficits. This is in contrast to reflux into a distal, cortical parent vessel, which may cause isolated focal deficits.

This was also noted in our experience (although we did not apply this term in this study ,AVMES score was published after study design)through achieving higher obliteration rate but not statistically significant association with embolization using distal ACA and PCA branches in order than other feeder territory. This term should be tested in the future on a larger scale.

Moreover, in our series we have found that whenever the cerebral AVMs have Dural supply, it is more safe to start embolization with meningeal branches as they are non-eloquent. Three cases in this

study have undergone embolization through meningeal branches of ECA achieving complete obliteration without complication. We routinely do 6 vessel diagnostic angiography in every AVM searching for dural supply and assessing the possibility of curative embolization using it.

To date, none of the published studies has discussed this strategy before. It is of importance to carefully detect any other IC – EC connections while performing such embolization.

In our study, we failed to establish statistically significant relation between arterial feeder pedicles regarding either the number or size and the embolization outcome or complications.

As regard to the number of arterial pedicle feeding AVM, this parameter was incorporated in all the scores proposed for endovascular grading by ***Feliciano et al.*** [16], ***Dumont et al.*** [17] and ***Lopes et al.*** [6] as a predictive of either obliteration rate or per procedural complications with difference in stratification of this number in relation to score.

According to ***Dumont et al.***[17] and ***Lopes et al.*** [6] embolization of each arterial pedicle essentially comprises a separate surgical approach as, with each embolization, the microcatheter must be removed and replaced for another arterial pedicle embolization. Whether performed during one prolonged procedure or in staged fashion, each microcatheterization and embolization carries technical risks of arterial dissection or wire perforation, as well as potential neurological damage. Thus, with an increasing number of arterial pedicles accessed the risk of procedural complications increases.

However, as we concluded before based on our experience the number of accessed pedicles and the number of feeding pedicles are not in direct mathematical relation as the number of accessed pedicle and hence the portion of nidus obliterated is dependent more on opening of inta nidal channels between different compartments. Onyx has the ability to diffuse from one compartment to another as well as reflux in other feeders with more obliteration rate. This is more evident while studying the new onyx embolization techniques as transvenous embolization or pressure cooker technique.

On the other hand, the size of arterial pedicle was incorporated only in Buffalo score and according to ***Dumont et al.***[17] ,a smaller vessel caliber will make catheterization-related complication more likely, as a more delicate vessel is more prone to injury during wire manipulation. This was also consistent with our study conclusion ***And strauss et al.*** [14]. We concluded that the key factor of the technique is the size of the feeders. If there are large readily accessible non eloquent vessels feeding the nidus, that can accommodate the stiff Onyx compatible microcatheters, complete obliteration can be achieved, and sometimes through a single feeder without complications. AVMs with multiple small or en-passage feeders emphasize limitations of embolization.

To summarize, endovascular embolization with Onyx is a powerful treatment tool; however, it requires considerable experience and knowledge in handling the microcatheters and embolization materials. Clinical judgment in patient selection is indispensible.

In many cases with favorable anatomy, curative endovascular treatment is appropriate and can achieve a high obliteration rate using embolization exclusively. Small superficial lesions (grades I–II) in non eloquent areas supplied by big arterial feeders are an ideal target for endovascular embolization using Onyx. In this group of patients, we had a high rate of complete obliteration with no significant morbidity. This is of course also true for other treatment options, as these kinds of lesions are attractive targets also for microsurgery and radiosurgery, with a low morbidity and mortality in all treatment modalities Treatment decisions in these cases should be based on vascular anatomy, surgeons experience and patient preference after reviewing the pros and cons of each treatment modality.

CONCLUSION

For the cases that are not fulfilling these criteria, embolization should be offered

as preparing step for other modality of treatment. In our experience, for curative embolization, the AVM should be small sized (< 3 cm), supplied by one vascular territory, with feeders that can tolerate reflux up to 2–3 cm, with clear proximal parts of the draining veins, and not located in deep structures.

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