

Use of Onyx (a patented ethylene-vinyl alcohol copolymer formulation) embolisation of cerebral arteriovenous malformations in Hong Kong: initial experience

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Objective To review the experience with Onyx embolisation of cerebral arteriovenous malformation.

Design Prospective study.

Setting A regional neurosurgical centre in Hong Kong.

Patients Data of patients with cerebral arteriovenous malformation who underwent Onyx embolisation over a 14-month period were prospectively collected.

Results Eleven sessions of Onyx embolisation were performed in nine patients with cerebral arteriovenous malformations, seven of which had ruptured. Total occlusion was achieved in three (33%) of the patients, and subtotal occlusion (over 80% occlusion) in three out of four with Spetzler-Martin grade-III/IV malformations. One patient developed mild permanent neurological deficit.

Conclusion Onyx embolisation of cerebral arteriovenous malformations is feasible in Hong Kong. Careful patient and target selection are important.

Introduction

Modern treatment of cerebral arteriovenous malformation (AVM) comprises the following interventions alone or in combination: microsurgical excision, stereotactic radiosurgery, and endovascular embolisation. Embolisation is practised in centres worldwide as well as in Hong Kong. Its purpose is to reduce AVM size to facilitate subsequent microsurgery and radiosurgery, or an anatomical cure. Until recently, standard endovascular treatment consisted of embolisation with particles or n-butyl-cyanoacrylate (NBCA) glue. Embolisation with particles alone has not been very effective, given the small-lumen flow-directed microcatheters used and the high recanalisation rate. The NBCA polymerises quickly in contact with ionic solutions, with the risk of microcatheter gluing, and thus the amount of glue injected per catheterization is limited. Frequently, multiple catheterizations of AVMs are necessary to achieve a high rate of occlusion. Onyx (ev3 Neurovascular, Irvine, CA, US) was introduced as a new embolic material for the endovascular treatment of cerebral AVMs. Onyx is non-adhesive, yet cohesive and precipitates slowly, which seems to be advantageous in AVM embolisation.^{1,2} Onyx was first introduced to Hong Kong on 13 October 2007. Here we present our local experience in the Prince of Wales Hospital over a 14-month period.

Methods

Patients

We prospectively collected data of all patients treated with Onyx for cerebral AVM in Prince of Wales Hospital, Hong Kong from October 2007 to December 2008 (Table 1). There were 11 sessions of Onyx embolisation of cerebral AVMs in nine patients. Seven patients underwent one session of embolisation and two underwent two sessions. The mean age of the patients was 30 years, with a range of 18 to 45 years. Most patients presented with haemorrhage (67%, 6/9). Two presented with epilepsy and one with headache. The mean follow-up of the cohort was 10 months.

Key words
Embolization, therapeutic; Intracranial arteriovenous malformations; Polyvinyls; Treatment outcome

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在香港使用獲專利的乙烯-乙醇共聚物配 方 (Onyx) 作腦動靜脈畸形的栓塞治療： 初步經驗

- 目的** 回顧使用Onyx作腦動靜脈畸形栓塞治療的經驗。
- 設計** 前瞻性研究。
- 安排** 香港一所腦外科中心。
- 患者** 前瞻性搜集分析14個月內接受Onyx栓塞治療腦動靜脈畸形的病人資料。
- 結果** 9名腦動靜脈畸形的病人接受了11次Onyx栓塞治療，其中7例動靜脈畸形破裂。3名病人（33%）完全閉塞，另4名Spetzler-Martin第三及第四級動靜脈畸形患者中，3名呈大部份閉塞（超過八成閉塞）。1名病人出現輕微的永久性神經損傷。
- 結論** 使用Onyx作腦動靜脈畸形的栓塞治療在香港是可行的。慎重選擇病人相當重要。

Cerebral arteriovenous malformations

There was one large cerebellar AVM, which recurred after radiosurgery. One patient had a left posterior temporal AVM associated with a middle cerebral artery aneurysm, and another had a left temporo-parieto-occipital AVM. Two patients had right frontal AVMs, and three had left occipital AVMs.

The size of these AVMs ranged from 1 to 5 cm (mean, 2.7 cm). Based on the Spetzler-Martin classification of AVMs,³ three (33%) were grade I, two (22%) were grade II, two were grade III, and two were grade IV. The grade-I and -II AVMs (5/9, 56%) had their embolisation with the intent to completely occlude the malformation if feasible. The grade-III and -IV AVMs (4/9, 44%) had their embolisation to reduce the

malformation's volume so as to facilitate subsequent microsurgery or radiosurgery.

Onyx liquid embolic agent

Onyx is a non-adhesive liquid embolic agent^{4,5} supplied in ready-to-use vials. Each vial contains ethylene-vinyl alcohol copolymer, dimethyl sulfoxide (DMSO), and tantalum. The copolymer dissolved in DMSO is prepared in three different concentrations: 6.0%, 6.5%, and 8.0%. The vials are kept on a shaker for at least 20 minutes to ensure proper mixing of the tantalum powder. The lower the concentration of the copolymer, the less viscous is the agent. Onyx concentrations of 6.0%, 6.5%, and 8.0% have viscosities of 18, 20, and 34 cP, respectively, and accordingly it is formulated as Onyx 18, Onyx 20, and Onyx 34. If the mixture comes into contact with aqueous solution, precipitation of the copolymer is initiated by diffusion of DMSO. This process begins on the surface while the core is still liquid, resulting in a soft, non-adherent mass. Therefore, Onyx has a lava-like flow consistency within blood vessels and does not fragment during injection. Onyx 18 is recommended for embolisation of any plexiform nidus and Onyx 34 for embolisation of large arteriovenous shunts. In our cohort, Onyx 18 was used as the embolisation agent in all patients, with the exception of one for whom Onyx 34 was used to embolise the fistulous component.

Embolisation techniques

All sessions of Onyx embolisation were carried out under general anaesthesia on a biplane angiographic unit.⁶ A 6-French (6F) arterial sheath was placed in the right femoral artery. Diagnostic cerebral angiography

TABLE I. Patient profiles

Sex/age (years)	Pathology*	Spetzler-Martin grade	Presentation	Complications of embolisation and outcome	3-Month outcome	Further treatment
M/18	Left parasplenic AVM	II	Haemorrhage	Nil	Good recovery	Radiosurgery
F/29	Left fronto-parieto-temporal AVM	IV	Epilepsy	Mild right upper limb weakness with complete recovery	Good recovery	Radiosurgery
F/45	Left temporal AVM	III	Haemorrhage	Nil	Good recovery	Surgery
M/28	Left temporo-parieto-occipital AVM	III	Headache	Expressive dysphasia with complete recovery	Good recovery	Radiosurgery
F/39	Left occipital AVM	II	Haemorrhage	Nil	Good recovery	Radiosurgery
M/33	Left occipital AVM/AVF/aneurysm complex	I	Haemorrhage	Nil	Vegetative state	Total occlusion by embolisation alone
M/18	Right cerebellar AVM	IV	Haemorrhage	Mild left-sided numbness	Good recovery	Surgery
M/33	Right frontal AVM	I	Haemorrhage	Nil	Good recovery	Total occlusion by embolisation alone
F/23	Right frontal AVM	I	Epilepsy	Nil	Good recovery	Total occlusion by embolisation alone

* AVM denotes arteriovenous malformation, and AVF arteriovenous fistula

was performed and a 6F guiding catheter was then inserted in either an internal carotid artery or a dominant vertebral artery, using a standard coaxial technique. A DMSO-compatible flow-directed microcatheter (Marathon, ev3 Neurovascular) was navigated to the nidus of AVM, with an aid of a 0.008-inch guidewire (Mirage, ev3 Neurovascular). Angiography was reviewed to ensure that the feeding pedicle could be occluded up to 2 cm retrogradely by the reflux of Onyx along the microcatheter. The microcatheter was flushed with DMSO and the dead space of the microcatheter was slowly filled with Onyx for no less than 40 seconds (40 seconds was chosen to avoid the DMSO bolus reaching the cerebral circulation). Then Onyx was slowly and progressively injected into the nidus under continuous visual control using biplane subtracted fluoroscopy. As soon as reflux was noted along the microcatheter or early embolisation of the draining vein was evident, the injection was stopped for 1 to 2 minutes and then resumed. The maximum reflux tolerated was 2 cm. Onyx injection times in our cohort lasted between 10 and 35 minutes. The microcatheter was removed using the technique of gradual increase in traction.

Results

In the five AVMs attempted for endovascular cure, three (3/5, 60%) achieved curative Onyx embolisation. The remaining two AVMs failed as an intranidal positioning of the microcatheter could not be achieved and resort to embolisation from a perinidal position became necessary. These two patients nevertheless achieved significant flow reduction and were further managed with radiosurgery. There was no procedural morbidity or mortality in these five patients, and in particular there was no procedural intracranial haemorrhage or instance of a stuck/retained microcatheter. Four patients returned to work/study. One patient remained dependent, which was related to the initial haemorrhage.

In the four patients with AVMs in whom maximal volume reduction was attempted, three (3/4, 75%) achieved a more-than-80% volume reduction. Two patients had transient neurological deficits (one had mild right upper limb weakness and one developed an expressive dysphasia); both deficits resolved within 1 month. One of these patients also developed a convexity-related subarachnoid haemorrhage evident on post-procedural computed tomography. Another patient had persistent mild left-sided numbness at the 1-month follow-up visit. There was no mortality or major permanent neurological deficit in this group of patients. One of them subsequently had radiosurgery and one underwent microsurgical excision. The other two patients were planned for microsurgery and radiosurgery, respectively. All four patients returned to work/study.

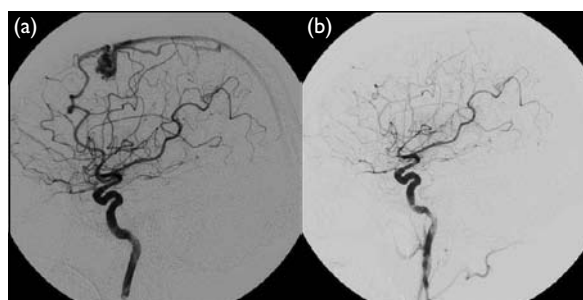


FIG 1. (a) Lateral view of the right frontal arteriovenous malformation before Onyx embolisation; (b) lateral view showing cure after embolisation

Case illustrations

Case 1

A 33-year-old man presented with headache and nausea. Computed tomography showed intraventricular haemorrhage and diagnostic cerebral angiography showed a frontal AVM (Fig 1a). Treatment options were discussed and the patient preferred an attempted embolisation cure. A single 1.2 mL Onyx embolisation completely occluded the AVM (Fig 1b). He remained well and was discharged 3 days after the procedure.

Case 2

A 28-year-old man presented with headache and magnetic resonance imaging showed a 5-cm left temporo-parieto-occipital AVM with superficial (cortical) and deep (straight sinus) venous drainage. He was referred for non-surgical management and planned for staged embolisation followed by radiosurgery. The first session of embolisation completely occluded the posterior circulation contribution to the AVM (Figs 2a, 2b). A second session of embolisation 3 months later through the left middle cerebral artery achieved a subtotal occlusion (Figs 2c, 2d). His course was complicated by a convexity-related subarachnoid haemorrhage and expressive dysphasia, which completely recovered within 1 month.

Discussion

The annual cumulative risk of intracranial haemorrhage from cerebral AVMs is estimated to be 4.6%, increasing to 7.5% in the first year after a haemorrhage.⁷ The aim of AVM treatment is total occlusion so as to prevent future haemorrhage, which may be achieved by microsurgery, radiosurgery, and embolisation, either alone or in combination. Availability of different treatment modalities is the key to successful AVM treatment. Microsurgery remains the standard treatment for ruptured AVMs located

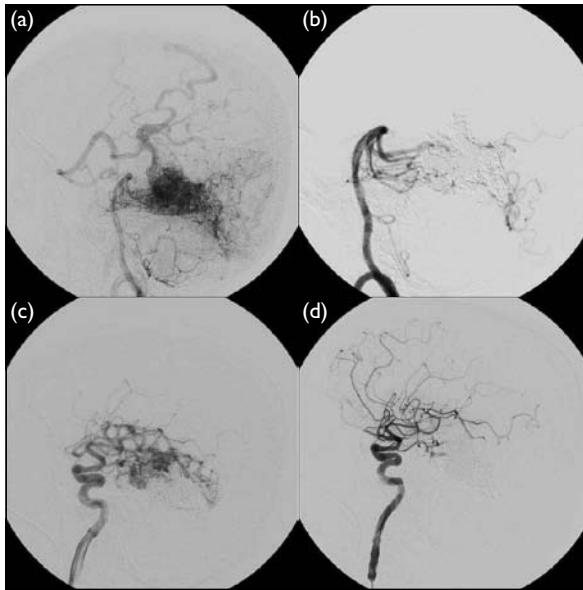


FIG 2. (a) Lateral view of posterior circulation contribution to the left temporo-parieto-occipital arteriovenous malformation (AVM) before Onyx embolisation; (b) lateral view showing no more posterior circulation contribution after first session of Onyx embolisation; (c) lateral view showing the left middle cerebral artery supply to the AVM before second session of Onyx embolisation; (d) lateral view showing subtotal occlusion of the AVM after second session of Onyx embolisation

in non-eloquent areas, while radiosurgery caters for small AVMs located in eloquent areas. Embolisation is employed by most local neurosurgeons as a supplementary tool or alternative treatment. In the field of endovascular treatment, Onyx embolisation is gaining popularity for its non-adhesive yet cohesive nature, and its associated long injection time. A review in the literature showed data to support

its efficacy in AVM cure and AVM size reduction (Table 2).^{4,6,8-14} In centres using Onyx embolisation alone as their primary treatment for cerebral AVM, complete occlusion rates as high as 49 to 54% have been reported, with a neurological morbidity of 8 to 8.5% and mortality of 3%. For the primary purpose of volume reduction, Onyx embolisation was reported to have an encouraging 50 to 85% average success rate with a 4 to 10% rate of neurological morbidity.

Although Onyx is non-adhesive, jamming of the microcatheter in the refluxing feeding artery pedicle can still lead to problems. Stuck (and subsequently broken and retained) microcatheters were described in earlier reported series. Strict adherence to reflux length as well as injection time is the key to avoiding these problems. A DMSO-compatible detachable catheter (Sonic, Balt, Montmorency, France) is available in the market and may be considered to be an alternative solution.

There are other limitations or disadvantages to Onyx embolisation. The degree of AVM occlusion achieved cannot be absolutely predicted before embolisation. With its high radio-opacity, the Onyx cast can over-project the rest of the nidus making it difficult to visualise the course of the Onyx being injected. This can theoretically result in unexpected entry of Onyx into the venous part of the malformation with possible catastrophic results. Moreover, the high radio-opacity may also make subsequent radiosurgery challenging, if the residual nidus does not stand out compactly. For large AVMs, the aim of embolisation is volume reduction without 'fragmenting' the nidus, and thus the residual nidus should be at the periphery of the Onyx cast and easily delineated during the planning of radiosurgery. In small AVMs not totally occluded by embolisation,

TABLE 2. Literature review of Onyx embolisation with the intent of endovascular cure and/or primary aim of volume reduction for subsequent microsurgery or radiosurgery

Case series	No. of patients	Angiographic cure	Permanent neurological deficit	Procedure-related death	Other technical complications (No. of patients)
Mounayer et al, ⁶ 2007	94	49% (26/53)	8.5% (8/94)	3.2% (3/94)	Retained microcatheter (4), distal rupture of arterial feeder (5)
Weber et al, ⁵ 2007	94	20% (19/94)	9.6% (9/94)	0%	Stuck microcatheter (9), distal perforation (4)
van Rooij et al, ⁴ 2007	44	16% (7/44)	4.6% (2/44)	2.3% (1)	Glued microcatheter (2)
Katsardis et al, ⁸ 2008	101	54% (28/52)	8% (8/101)	3% (3/101)	Stuck microcatheter (1)
Panagiotopoulos et al, ⁹ 2009	82	24.4% (20/82)	3.8% (3/82)	2.4% (2/82)	-
Song et al, ¹⁰ 2007	70	18.6% (13/70)	7.1% (5/70)	1.4% (1/70)	-
Jahan et al, ¹¹ 2001	23	Average: 63%*	4% (1/23)	0%†	-
Weber et al, ¹² 2007	47	Mean: 85±18%*	Disabling: 9%; non-disabling: 21%	0%†	Stuck microcatheter (4), vessel perforation (5)
Natarajan et al, ¹³ 2008	28	Average: 74±18%*	1/28 (3.6%)	0%†	Stuck microcatheter (2), vessel perforation (1)
Velat et al, ¹⁴ 2008	20	Median: 50±25%*	10% (2/20)	5% (1/20)†	-

* Data of nidus reduction are shown

† Data of mortality are shown

the whole AVM nidus and the Onyx cast should be included for radiosurgery planning, if at all feasible.

Whether prior embolisation with Onyx affects the complete obliteration rate is still to be investigated. The effect of prior glue embolisation on the radiosurgery complete obliteration rate remains controversial; some authorities report an improved obliteration rate and others a reduced rate.¹⁵⁻²⁰ This uncertainty is probably due to the difficulty in interpretation of the nidal contour, for which reason generous planning to include some of the adjacent embolised portion of AVM is recommended.

Microsurgical excision after Onyx embolisation had been quoted as conversion of AVM surgery to meningioma surgery, with markedly decreased vascularity. There are two features that should be recognised for microsurgery after Onyx embolisation. First, that such embolisation makes it difficult to shrink the AVM, in contrast to cases in which no embolisation is performed.¹³ Second, that electrocautery-induced ignition of Onyx has been reported for monopolar diathermy and high energy settings of bipolar diathermy (≥ 35 Malis units), which fortunately did not affect the normal setting employed for microsurgical excision of cerebral AVMs.²¹

Even though Onyx and NBCA have been used for cerebral AVM embolisation, it is difficult to compare the two directly outside a randomised controlled trial setting. It is obvious that these two agents differ in their physical properties, and in aspects such as cost and microcatheter compatibility. Moreover, expertise in manipulating these agents played an important role in selection. Velat et al¹⁴ tried to compare NBCA and Onyx, and concluded Onyx embolisation required an increase

in procedural time with no difference in operative blood loss. However, the retrospective nature with unknown case selection (60 patients received NBCA embolisation alone, 20 received Onyx embolisation alone, and eight others who underwent NBCA plus Onyx embolisation) made comparison impractical. The reasons for recurrence after glue embolisation are pedicle embolisation and recanalisation of the thrombosed portion (induced by glue). Onyx nidal embolisation theoretically eliminates this possibility. In the literature, the recurrence rate of Onyx AVM embolisation has been reported to be between 0% and 4.8%, mainly during the initial 3 to 4 months.^{5,6,9} In our three patients who achieved total occlusion, there was no evidence of recurrence based on 6-month digital subtraction angiography in two, and magnetic resonance angiography after 3 months in the other. Given Onyx's non-adhesive penetrating properties, we believe that it will prove to be a promising agent for cerebral AVM embolisation.

Declaration

The authors declared no conflicts of interests.

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