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Analysis on the effect and prognostic factors of cerebral arteriovenous malformations (AVM) after endovascular embolization combined gamma knife surgery.

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Abstract

Background: Brain Arteriovenous Malformation (BAVM) was induced by the congenital development abnormality of partial vascular anomaly differentiation. Better prognostic factors should be developed by our researchers.

Objective: To analyse the clinical and follow-up materials about Arteriovenous Malformation (AVM) treated by endovascular embolization combined with radiosurgery (Gamma Knife Surgery, GKS), and discuss the efficacy and influencing factors of AVM treatment, thus providing a reference for the clinical treatment of AVM.

Methods: A summary for 55 cases of AVM patients having received the endovascular embolization combined with GKS in the Department of Interventional Neuroradiology, Beijing Tiantan Hospital from April 2004 to September 2011 and having rather complete follow-up materials is carried out, and a statistical analysis is conducted for the focus volume size, Spetzler Martin grade, impact characteristics of malformation vascular mass, and the influence of radiation dose and other variables on patients' treatment efficacy.

Results: The complete cure rate of patients after combined treatment in this research is 31.25%. The mean volume before embolism is 16.68 ± 16.22 cm^3 (range: 0.75-75 cm^3). Among 17 AVM patients whose initial symptom is epilepsy, 8 have clearly reduced the epileptic seizure frequency or become completely recovered after GKS. Among the 37 patients with image follow-up, the overall cure rate is 31.25%. The risk factor prediction of bleeding complications after endovascular embolization combined with GKS is of statistical significance: The AVM volume (P=0.039), the number of supply artery (P=0.048), and the draining vein phlebostenosis (P=0.01). The long-term prognosis influencing factors of endovascular embolization combined with GKS were: mRS prior to admission (p=0.011), follow-up time (p=0.013).

Conclusion: Endovascular embolization combined with GKS is a safe and effective method for AVM, but it cannot completely eliminate embolism malformation mass, so the risk of rupture haemorrhage still exists.

Keywords: BAVM, Onyx embolization, GKS, Complete obliteration rate, Complications.

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Introduction

Brain Arteriovenous Malformation (BAVM) is a result of the congenital development abnormality of partial vascular anomaly differentiation in the 4th-8th week of the embryo. AVM rupture haemorrhage may lead to 5-10% mortality and 30-50% morbidity. The main purpose of AVM treatment is to eliminate the risk of rupture haemorrhage and relieve various clinical symptoms caused by steal [1-3]. Main methods for the treatment of BAVM are: micro-surgery, endovascular therapy, stereotactic radiotherapy and joint treatment of the above three methods. Surgical resection is the most classic and most common treatment [4]. With the continuous development of endovascular treatment technology, endovascular treatment has become one of the most important measures for the treatment of BAVM at home and abroad currently [5].

Endovascular embolism has advantages like small trauma and repeatability, and it has disadvantages like low cure rate, and the long-term co-use with surgeries or radiotherapy. Stereotactic radiosurgery refers to the use of modern stereotactic techniques and computer technology to gather large doses of high-energy proton beams from multiple angles and directions on a target tissue, thus reaching the purpose of destroying targets for the treatment of disease [6]. GKS is the most common treatment means, and its mechanism is to

promote the endothelial cell proliferation of malformation vessels, wall thickening, stenosis, and final memory vascular closure, so as to reach the purpose of treatment. After treatment, the occlusion rate is between 50% and 80%, and major complications include radioactive brain oedema, brain necrosis, and haemorrhage caused before the incomplete occlusion of malformations vessels [7].

Since onyx was not approved to be used domestically until 2003, there are few researches about the efficacy and influencing factors of onyx endovascular embolization combined with GSK on BAVM treatment [8]. This study aims to analyse the clinical and follow-up materials about AVM treatment by endovascular embolization combined with GSK, and discuss the efficacy and influencing factors of AVM treatment, thus providing a reference for the clinical treatment of AVM.

Materials and Methods

Patients' materials

Retrospectively collection and analytical study on 55 AVM patients treated by endovascular embolization combined with GSK in the Department of Interventional Neuroradiology, Beijing Tiantan Hospital, from April 2004 to September 2011 were conducted. Details of patients and basic AVM characteristics were shown in Table 1.

Table 1. *The basic characteristics of patients and arteriovenous malformation.*

Characteristics	Case no. (%)
Case no.	55
Gender	
Male	28 (50.9)
Female	27 (49.1)
Age (year)	
Average	29.9 ± 11.3
Range	8-50
Position	
Lobes (frontal/temporal lobe, parietal lobe/occipital lobe)	41 (74.5)
Corpus callosum	4 (7.3)
Basal ganglia	1 (1.8)
Thalamus	3 (5.5)
Cervelet	5 (9.1)
Brainstem	1 (1.8)
Depth	
Cortex	31 (56.4)
Deep	24 (43.6)
Volume (cm^3)	
Average	16.68 ± 16.22
Range	0.75-75
Size (cm)	
<3 cm	15 (27.3)
3-6 cm	39 (70.9)
>6 cm	1 (1.8)
Supply artery (>2 mm)	
Single	15 (27.3)
Multiple	40 (72.7)
Venous drainage	
The shallow drainage	30 (54.5)
Deep+shallow drainage	12 (21.8)
Deep drainage	13 (23.7)
Venous drainage number	
Single	2443.6
Multiple	3156.4
Merged aneurysm	18 (32.7)
Sunouchi	15 (27.3)
Blood flow correlation	3 (5.5)
Combined arteriovenous fistula	2 (3.6)
Varicose vein	10 (18.2)
Sm classification	
I	5 (9.1)
II	15 (27.3)
III	21 (38.2)
IV	13 (23.6)
V	1 (1.8)
Symptoms	
Bleeding	24 (43.6)
Bleeding+Headache epilepsy	3 (5.5)
Epilepsy	14 (25.5)
Headache	9 (16.4)
Other (cranial nerve dysfunction/numbness/strength decrease/dizzy/vision loss)	4 (7.2)
Asymptomatic	1 (1.8)

According to the MRI or DSA technology, the AVM volume size before embolism was calculated. After partial embolism, the 3D-MRI simulation method is used to estimate the residual volume before receiving GSK by patients. The inclusion criteria: If the patient receives DSA or MRI re-examination in five years after the embolism and GSK treatment, and the

results show the malformation mass has completed been healed; the exclusion criteria: those receiving less than 5 years of clinical follow-up [9,10].

Embolism materials

Onyx was taken as a kind of embolic material. In order to ensure the relatively uniformed treatment materials, patients who have received NBCA, spring ring or segment embolism are not involved before the Onyx embolization. In addition, before the embolization treatment, there's no surgical treatment history of patients.

Treatment methods

Selection of treatment schemes [11,12]: If the AVM is with rupture haemorrhage, the AVM anatomy characteristics presented by the image materials (DSA or MRI) and patients' will should be taken as the basis as far as possible. Through the preoperative evaluation by the surgical treatment team, if the surgical treatment risk is large or patients ask for endovascular embolization actively, then the endovascular embolization treatment way will be adopted; when the endovascular embolization AVM is incomplete, the radiosurgery (GKS) will be used as a kind of auxiliary therapy.

If the AVM was not ruptured, then the treatment scheme should be selected in accordance with the history of patients' present illness, the history of past diseases, and relevant risks of treatment. Among the case database, 1 case shows no AVM rupture due to the post-injury routine examination, and the rest 27 cases without AVM rupture are all symptomatic AVM. After evaluating the AVM bleeding risk, patients or their families are told about the illness and the intervention treatment is selected according to their own willingness. Through the preoperative risk evaluation by the nerve surgical treatment team, the endovascular embolization is taken as the prime treatment scheme when the surgical risk is huge or patients selects embolization actively; when the endovascular embolization AVM was incomplete, the radiosurgery (GKS) will be used as a kind of auxiliary therapy.

Onyx endovascular embolization principles and process [13,14]: Volume and blood supply: If the volume of AVM was small and there were few supply arteries, the complete embolization should be done as far as possible. For AVM with large volume and complex blood supply, the partial endovascular embolization way should be adopted, and radiosurgery (GKS) should be used jointly after surgery as a kind of auxiliary therapy.

All patients receiving the treatment were operated with general anaesthesia. The Onyx injection time, the diffusion, reflux and molding in the malformation mass were observed closely. If necessary, repeated angiography should be done.

Stereotactic radiosurgery (SRS) treatment [15,16]: This study mainly carries out the radiosurgery treatment with the help of the Leksell Gamma Knife PerfexionTM system, and its basic steps are shown as follows:

If patients are children, then try to use the general anaesthesia way; if patients are adults, the local anaesthesia should be adopted. After the stereotactic radiotherapy, a stereotactic ring should be removed from the patient's head. When the patient gets awake, they can be discharged and return to normal life.

Follow-up: The surgical process, embolization related complications, GKS treatment process, GKS radiation complications, MRI, whole cerebrovascular angiographic and clinical follow-up results of patients who have received the endovascular embolization treatment and radiosurgery (GKS) treatment are all collected in the arteriovenous malformation database. The clinical follow-up was completed through the outpatient and phone calls. Both of MRI and DSA imaging result were evaluated by specialist physician who came from the GKS center and nerve invasion technology department. If AVM is still not healed after 3-5 years, further therapeutic intervention will be considered.

The formula of annual bleeding rate during the follow-up: "annual bleeding rate (%) = (case number of bleeding/risk years*) × 100%". (*Risk years refer to the time from the completion of radiosurgery to the complete recovery or the last non-bleeding clinical follow-up.)

Statistical analysis

The SPSS17.0 statistical analysis system was used for statistical analysis of various factors. The chi-square test is used for enumeration data, and t-test was used for measurement data. Logistics regression analysis was used for statistics of risk predictive factors.

Results

Imaging results of targeted embolism

Imaging features of AVM after embolization and embolization operation were shown in the following Table 2. According to bleeding hazard factors combined by AVM (interior aneurysm, hemodynamic aneurysm and arteriovenous fistula), targeted embolism is conducted for these risk factors. For partial located at (or close to) important perforating supply arteries or having huge treatment difficulties due to the above high risk factors, partial embolization is only conducted specific to AVM.

Table 2*. Results and characteristics of endovascular embolization.*

Information embolization	Results (%)
Volume before embolization (cm^3)	
Average	16.68 ± 16.22
Range	0.75-75
Volume after embolization (cm^3)	
Average	8.7
Range	0.57-39

SM classification before embolization	
Average	2.8
Range	1-5
SM classification after embolization	
Average	1.4
Range	1-2
Onyx (Volume (ml))	
Classification	1.87
Median	±1.61
Range	0.2-7.4
Decreased volume of AVM	
<50%	23
50-90%	29
>90%	3
AVM shape after embolization	
Concentrated	51
Dispersion	4
Merge the nest aneurysm (an)	15 (27.3%)
Targeted embolization	13
None embolization	2
Combined arteriovenous fistula	3 (5.5%)
Targeted embolization	3
None embolization	0
Combined arteriovenous fistula	4 (7.3%)
Targeted embolism	4
Partial embolism	0

Relevant complications about endovascular embolization operation

Complications related to the endovascular embolization treatment are caused by embolism operation. Clinical complications appeared during the endovascular embolization surgery or before the GKS treatment after embolism are shown in Table 3 and Table 4.

Table 3. *Related complications after endovascular embolization operation.*

Complication	Number (%)
Temporary complications	
Bleeding	2 (3.6%)
Muscle weakness	2 (3.6%)
Muscle weakness	1 (1.8%)
Diplopia	1 (1.8%)
Permanent complications	
Blood clots to lower strength	1 (1.8%)
Leave a tube	1 (1.8%)

Table 4. *Haemorrhagic complications after embolization.*

No.	Gender	Age	Symptom	Clinical manifestation	Bleeding time	CT performance	Reason	Prognosis follow up
1	Female	40	Epilepsy	Headache	First days after embolization	SAH	Aneurysm without thrombus	Good, epilepsy controlled by drug
2	Female	33	Bleeding	Headache	Immediately after embolization	Ventricular haemorrhage	Drainage vein stenosis	Recovery well

Cure rate

Among 55 AVM patients receiving Onyx embolization combined with GKS treatment, 37 (67.3%) have taken the DSA or MRI re-examination after radiosurgery. According to CT, it is verified that 2 cases died because of AVM bleeding (unhealed). The image follow-up shows that the AVM of 10 cases has been eliminated completely, and the cure rate of joint treatment is 31.25%.

Improved clinical symptoms

Clinical symptom follow-up has been conducted for all of the 55 patients. According to the postoperative and follow-up mRS score results, the specific follow-up information compared to that in the initial treatment is shown in the following Table 5.

Table 5. *Clinical follow-up results after GKS treatment.*

Follow-up data	Value (%)
Clinical follow-up time (day)	
Average	2435.91 ± 727.64
Range	369-3840
Changes of clinical symptoms after GKS treatment	
Significantly improve	10

Keep stable	43
Haemorrhage	2
MRS score at the time of treatment	
0	45
1	5
2	3
3	1
4	1
MRS score at follow-up	
0	51
1	1
2	1
6	2

Risk factor analysis of haemorrhage complications

According to statistical analysis results, it is considered that huge volumes, multiple supply arteries, and stenosis draining veins are risk predictive factors causing haemorrhage complications after single joint treatment, as shown in Table 6.

Table 6. *Analysis of risk factors for bleeding complications during follow-up.*

Risk factors	P
AVM deep	0.121
Volume	0.039
Number of feeding arteries	0.048
Drainage vein stenosis	0.01
Edge measurement	0.146
Center measurement	0.132
VARS score	0.201
Deep venous drainage	0.14

Discussion

BAVM is a common vascular disease of neurosurgery. Its onset age is mainly between 16 and 35, with the proportion of males slightly higher than that of females. The lesion is mainly because of the direct connection of cerebral arteries and vein which leads to the brain hemodynamics disorder, thus causing clinical symptoms such as epileptic seizure, intracranial haemorrhage or progressive dysneuria. Brain malformation mass rupture haemorrhage is a severest symptom with high mortality [17-19]. The main purpose of curing BAVM is to cure the epilepsy, eliminate headache, prevent bleeding, avoid steal and recover neurologic functions.

Currently, the mere use of endovascular embolization AVM for BAVM treatment may lead to risks such as normal perfusion pressure breakthrough. Therefore, the treatment of AVM requires the close collaboration of a variety of programs. For endovascular embolization combined with GKS, it's more common to conduct embolization treatment before GKS treatment. Some also choose radiotherapy before embolization. The purpose of embolization before radiotherapy is to eliminate malformation vascular masses insensitive to radiation therapy and cure the high-flow aneurysm or arteriovenous fistula. Embolization after radiotherapy is generally used for AVM whose mere radiosurgery fails. Cobin et al. conducted research on the endovascular embolization and GKS treatment through 125 cases of patients. The partial embolization AVM of 65% can obtain complete occlusion eventually [20]. However, the effect of endovascular embolization combined with GKS is still controversial. According to some studies, the effective rate of embolization before radiotherapy is even much lower than other treatment ways, which is also not conductive to the occlusion of malformation vascular mass.

As for incomplete occlusion of patients after endovascular embolization combined with GKS by this research, the reasons are summarized below: (1) For cerebral arteriovenous malformation mass with large volume, the volume of residual part after endovascular embolization is still large or located deep in the brain functional area. The gamma knife radiation dose is limited or the complete occlusion degree cannot be reached by certain doses; (2) The Onyx does used for endovascular embolization treatment cannot be fully closed for supply arteries or postoperative vascularization after embolization; (3) For non-uniform type AVM or shunt type AVM, the occlusion rate is usually low.

There are deficiencies in the following aspects of the research: Due to the different selection of patients, the collected data results are hard to be compared with results of the mere radiotherapy, such as AVM size, with or without bleeding history, and anatomical structure. This research method is a single-center retrospective study, and the objects are patients receiving the embolization with the same materials as well as GKS treatment, so the sample quantity is relatively small. The haemorrhage after SRS is diagnosed by CT only when patients show headache, while it is hard to discover the asymptomatic haemorrhage through the follow-up MRI. Therefore, there is a possibility of missed diagnosis of asymptomatic haemorrhage.

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