RESEARCH ARTICLE

Clinical Effectiveness of Preoperative Embolization for Cerebellar Hemangioblastoma

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Abstract

The cerebellar hemangioblastoma (CHB) has an abundant blood supply and deep anatomical location. Complete surgical resection is generally very difficult. This study investigated the safety and effectiveness of preoperative embolization followed by surgical resection of CHB in a large cohort of patients. A database of 125 CHB patients with surgical resection in Beijing Tiantan Hospital between July 2006 and July 2012 was reviewed. Of those, 46 cases (experimental group) received preoperative embolization, 79 cases (control group) underwent surgery without embolization. Patient demographics, tumor size, duration of surgery, blood loss, blood transfusion, complications and follow-up results were collected and analyzed retrospectively. In the experimental group, the Kamofsky score (KS) was 80-100 in 40 cases (86.9%), 40-70 in 4 cases (8.7%), and below 40 in 2 cases (4.3%). Among 31 cases with follow-up, KS was 80-100 in 27 cases (87.1%), 40-70 in 2 cases (6.5%), and 0 in 2 cases (6.5%). In control group, KS was 80 -100 in 65 cases (82.2%), 40-70 in 6 cases (7.6%), 10-30 in 3 cases (3.8%), and 0 in 3 cases (3.8%). Among 53 cases with follow-up, KS was 80-100 in 44 cases (83.0%), 40-70 in 4 cases (7.5%), 10-30 in 1 case (1.9%), and 0 in 4 cases (7.5%). There were statistically significant differences between the experimental and control groups in tumor size, duration of surgery, amount of intraoperative blood loss and transfusion (p <0.01). However, complications (p = 0.31) and follow-up results (p = 0.76) showed no significant differences between groups. Selective preoperative embolization of those CHB patients with richer blood supply, higher hemorrhage risk, is safe and effective, and is a reliable adjuvant therapy for complete surgical resection of CHB.

Keywords: Hemangioblastoma- embolization- surgical resection

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Introduction

Hemangioblastoma (HB) is a rare, benign tumor of the central nervous system, most commonly seen in the cerebellar hemispheres, followed by cerebellar vermis, the fourth ventricle, brainstem and spinal cord. It accounts for 1.5 % -3% of intracranial tumors and 8% -12% of posterior fossa tumors (Browne et al., 1976; Ogiwara et al., 2003; Pereda Rios et al., 2012). Cerebellar Hemangioblastoma (CHB) typically occurs in the posterior fossa, and is difficult for surgical resection due to its deep location. In addition, the tumor and surrounding tissues are generally highly vascular, have extremely abundant blood supply, and are prone to excessive intraoperative hemorrhage, which can hinder the complete resection of the tumor, and thus increase the risk of postoperative disability, mortality and recurrence (Chun et al., 2010; Munyon et al., 2011).

Currently, many published reports suggested the treatment of CHB should include embolization of feeding artery prior to complete resection of the tumor to reduce blood loss. Several available published data also showed that preoperative embolization was a safe and effective adjuvant therapy(Djindjian, 1986; Standard et al., 1994; Krishnan et al., 2006; Cornelius et al., 2007; Agrawal et al., 2010). However, the reports of preoperative embolization of CHB are still relatively rare, and most of them were individual case reports. A large comparative study of the CHB surgical treatment with and without preoperative embolization remains lacking. Therefore, to the extent that we know, the safety and effectiveness of preoperative embolization in CHB treatment has yet to be confirmed (Standard et al., 1994; Krishnan et al., 2006; Cornelius et al., 2007). A study that compares surgical time, intraoperative blood loss and blood transfusion, clinical efficacy and incidence of complications between patients underwent surgical resection with and without preoperative embolization is essential to evaluate the risk and benefits of preoperative embolization in the surgical treatment of CHB.

In this study, we conducted a retrospective analysis

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Table 1. Patients' Demographic, Tumor Characteristics and Prognosis by Study Group

	Experimental group	Control group	*P* value
Number of Cases	46	79	
Gender			
Male	34(73.9%)	59(74.7%)	>0.05
Female	12(26.1%)	20(25.3%)	
Age (Mean±SD)	43±12	44±12	
Tumor size (mm)	29	21	<0.001
Surgical Time (h)	7.6	8.4	<0.001
Intraoperative blood loss (ml)	484	976	<0.001
Blood transfusion (ml)	386	969	<0.001
Complication	8(17.4%)	20(25.3%)	0.305
Embolic	1(2.2%)	0(0%)	
Surgical	7(15.2%)	20(25.3%)	

of 125 CHB patients, largest cohort among all published reports so far, to explore the safety and effectiveness of preoperative embolization as an adjuvant therapy for CHB.

Materials and Methods

Study population

A total of 125 CHB patients underwent complete surgical resection in Beijing Tiantan Hospital between July 2006 and July 2012. Of them, 46 cases received preoperative artery embolization, including 32 males and 14 females, and their average age was 43 ± 12 years (range 9-58 years). Seventy nice cases underwent surgical resection without preoperative embolization, including 59 males, 20 females, and their average age was 44 ± 12 years (range 10-61 years) (Table 1).

Eligibility criteria

Inclusion criteria were as follows: patients were diagnosed with CHB using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography (DSA); the nature of the tumor was substantive and patients underwent surgical resection in our hospital. Exclusion criteria (patients with any one of the following criteria were excluded): (1) HB not located in cerebellar hemispheres, such as those in the cerebellar vermis, the fourth ventricle, brainstem, cerebellopontine angle, medulla oblongata, spinal cord; (2) the nature of tumor was cystic; (3) patients did not undergo surgical intervention.

Study group

Experimental groups consisted of eligible patients who received embolization prior to the surgery; control group consisted of eligible patients who did not undergo preoperative embolization. (note: imaging data from all patients were reviewed by a highly experienced neurosurgeon and a senior radiologist together. If data suggested rich blood supply to the tumor and high risk of intraoperative bleeding, the patients were assigned to receive preoperative embolization).

Preoperative embolization

Embolization material: For embolization, we used EncheIon 10 (Ev3, USA), Marathon microcatheter (Ev3, USA), Silverspeed10 (MTI, USA), mirage008 microguidewire (Ev3, USA), different types of detachable coils, Polyvinyl alcohol (PVA, 250-350um) and N-butyl cyanoacylate (NBCA, Histoacryl, Germany) and ethylene - vinyl alcohol copolymer (ONYX, Ev3, USA).

Table 2. Preoperative Embolization in the Experimental Group

Embolic material	Complete occlusion	Most occlusion	Partial occlusion	Total
ONYX	12 (63.2%)	5(26.3%)	2(10.5%)	19(41.3%)
14	7(50%)	6(42.9%)	1(7.1%)	14(30.4%)
GDC±PVA	6(46.2%)	4(30.8%)	3(23.1%)	13(28.2%)
	25(54.3%)	15(32.6%)	6(13.1%)	46(100%)

Embolization process: Patients were maintained under general anesthesia. A cerebral angiography was performed to investigate the tumor feeding artery and venous drainage. Using the road-mapping technique, microcatheter was advanced to tumor end of feeding artery. Superselective angiography was performed to avoid the involvement of blood vessels in normal tissue. Then, according to the vascular diameter, blood flow velocity, blood circulation time and tumor staining, embolization was proceeded with diluted NBCA biological glue, ONYX biological glue and / or a small amount of PVA particle as contrast agent. Post-embolization arteriography was also performed to demonstrate the obliteration of the vasculature.

Surgical Staff: Preoperative embolization was conducted by 2 experienced neurointerventionalists together. Tumor resection was performed by 2 senior neurosurgeons, with the assistance of experienced attending physicians.

Data analysis: In this study, statistical analysis was performed using SPSS (V19.0). Pearson X2 test was used to compare patients' age, gender, rate of complications and clinical effects between the experimental and control groups. Rank test was used to compare the tumor size, surgical time, and amount of intraoperative blood loss and blood transfusion between 2 groups.

Results

Embolization in experimental group

ONYX was used for embolization in 19 cases, one of which developed intracranial hemorrhage after surgery. Immediate post-embolization angiography showed complete occlusion in 12 cases (63.2%), most occlusion in 5 cases (26.3%), partial occlusion in 2 cases (10.5%). NBCA was used for embolization in 14 cases, and there was no intracranial hemorrhage developed after surgery. Immediate post-embolization angiography showed complete occlusion in 7 cases (50%), nearly occlusion in 6 cases (42.9%), and partial occlusion in 1 case (7.1%). GDC ± PVA was used for embolization in 13 cases without postoperative intracranial hemorrhage. Immediate post-embolization angiography demonstrated complete occlusion in 6 cases (46.2%), most occlusion in 4 cases (30.8%), partial occlusion in 3 cases (23.1%). Among all 46 patients underwent preoperative embolization, complete occlusion was achieved in 25 cases (54.3%),

Table 3. Follow-up Results by Study Group

	Experimental group	Control group	*P* value
KPS* at follow-up (4 categories)			
80-100 points	27(87.1%)	44(83.0%)	
40-70 points	2(6.5%)	4(7.5%)	
10-30 points	0(0%)	1(1.9%)	
0 points	2(6.5%)	4(7.5%)	
KPS at follow-up (2 categories)			
80-100 points	27(87.1%)	44(83.0%)	0.759
0-70 points	4(12.9%)	9(17.0%)	
Complications related to HB	3(9.7%)	8(15.1%)	
Follow-up rate	31(67.4%)	53(69.7%)	

KPS, Kamofsky prognostic score

followed by most occlusion in 15 cases (32.6%), and partial occlusion in 6 cases (13.1%). There was 1 patient developed treatment-associated thrombotic complication (2%) (Table 2).

Surgical resection

In experimental group, complete resection was achieved in 45 patients, 95% resection in 1 patient. There was no adjacent brain tissue damage. The mean operation time was 7.6 h, average intraoperative blood loss was 484ml (range 100-2240 ml), and average amount of blood transfusion was 386ml. Among patients achieved complete occlusion by preoperative embolization, intraoperative blood loss ranged between 100-1080 ml. All 18 cases who lost blood between 100-400 ml did not require blood transfusion. Among patients achieved most occlusion before sugery, intraoperative blood loss ranged between 130-2240 ml. In 8 cases whose blood loss was between 130-400 ml, blood transfusion was not required. For patients achieved partial occlusion preoperatively, intraoperative blood loss ranged between 340-1970 ml, all but one patient required blood transfusion. Thirty nine patients were free of serious complication after the surgery, 4 patients developed postoperative hydrocephalus, and 3 patients experienced intracranial hemorrhage. All patients were discharged 7-16 days after tumor resection. KS at discharge was between 80-100 in 40 cases (86.9%), 40-70 in 4 cases (8.7%), and 30 or below in 2 cases (4.3%). No patient died at discharge. In control group, visibly complete resection was achieved in 71 patients with no adjacent brain tissue damage. For the remaining 8 cases, due to excessive intraoperative bleeding and obliteration of surgical planes, 3 cases had 95% of tumor resected, 4 cases had 80% of tumor resected, and 1 case with only 60% of tumor resected. In addition, 6 cases experienced damage to the adjacent normal brain tissue. The average operation time in control group was 8.4 h, average blood loss was 976 ml (range 280-3240 ml), and average amount of blood transfusion was 969 ml. Fifty nine patients were free of serious postoperative complications, 8 cases developed postoperative hydrocephalus, 6 cases had intracranial hemorrhage, and 6 cases experienced serious complications due to adjacent brain tissue damage. All patients were discharged 9-21 days after the tumor resection. KS at discharge was between 80-100 in 65 cases (82.2%), 40-70 in 6 cases (7.6%), 10-30 in 3 cases (3.8%), and 0 in 3 cases (3.8%). There were statistically significant differences between the experimental and control groups on tumor size, duration of surgery, amount of intraoperative blood loss and transfusion (p <0.01). There was no significant difference between two groups on the incidence of complications (p = 0.31) (Table 1).

Follow-up results

The average follow-up time was 12.9 months (range 6-74 months). Of 125 patients, follow-up was successful in 84 patients. Of them, 31 were from the experimental group, with an average follow-up time of 13.8 months and resulting follow-up rate of 67.4% (31/46). The remaining 53 cases were from the control group, with an average follow-up time of 12.4 months and resulting follow-up rate of 69.7% (53/76).

In the experimental group, at follow-up the KS was between 80-100 in 27 cases (87.1%), 40-70 in 2 cases (6.5%), and 0 in 2 cases (6.5%). Of the 2 cases that showed poor follow-up results, there was no significant change of nerve function from the time of discharge in one case, and in another case the patient experienced cerebral infarction and subsequent developed moderate disability. Two patients died during the follow-up, one from the recurrence of HB 32-month after the surgery, and one from lung cancer. Three out of 4 disabled or fatal cases were related to HB. In the control group, at follow-up the KS was between 80-100 in 44 cases (83.0%), 40-70 in 4 cases (7.5%), 10-30 1 case (1.9%), and 0 point in 4 cases (7.5%). Eight out of 9 cases with poor prognosis were related to HB (15.1%). There was no significant difference between the experimental and control groups on the follow-up results (p = 0.76) (Table 3).

Discussion

CHB are substantive tumors with low incidence of spontaneous intracranial hemorrhage. However, due to rich blood supply of the tumor, hemorrhage during the resection surgery could be serious and sometime even life-threatening. In addition, excessive intraoperative bleeding can also obliterate surgical plane, cause accidental damage to the adjacent nerve tissue, and hinder the completer resection of the tumor, resulting in a recurrence rate of up to 25% (Hussein, 2007; Zywicke et al., 2012). Therefore, to improve the surgical success, reduce the incidence of complications and postoperative recurrence rate, preoperative embolization becomes critical. Currently, in order to reduce blood loss, preoperative embolization has been widely adopted in the surgical treatment of various types of tumors characterized with rich blood supply. Several clinical studies have also reported the main advantages of preoperative embolization: 1) preoperative embolization of the tumors with rich blood supply (such as meningiomas and cerebral arteriovenous malformations) can achieve a high success rate, help reduce permanent complications and mortality (Ellis et al., 2011; Latorzeff et al., 2012); 2) preoperative embolization of feeding arteries can interrupt blood supply and lower tumor tissue blood circulation, thus decrease the intraoperative blood loss and obtain a clear surgical plane, which can then help shorten the surgical time and postoperative hospital stay.

However, preoperative embolization may also increase the risk of embolization-associated intracranial hemorrhage and postoperative cerebral ischemic stroke (Munyon et al., 2011; Murai et al., 2012).

With the application of microcatheter, microguidewire and other new materials as well as the development of high-resolution angiography and three-dimensional rotational revascularization techniques, preoperative embolization of CHB is becoming popular (Horvathy et al., 2011; Sakamoto et al., 2012). Currently, the most commonly used embolic materials for CHB embolization were physical embolic material (such as balloon and coils), PVA particles and liquid embolic agents (such as ONYX, NBCA). Because the spring ring and balloon are difficult to reach proximal end of tumor feeding artery, the rate of complete embolization is very low. So in our hospital, we used only PVA particles, ONYX and NBCA. PVA particles, at the diameter of 250-350um, theoretically should have a high success rate of reaching the proximal end of tumor feeding artery, but Sorimachi et al (Sorimachi et al., 1999) reported the complete occlusion rate was only 14% with the use of PVA particles. In this study, patients received PVA particles also showed lowest rate of complete occlusion (Table 2). ONYX and NBCA are all liquid embolic agents, can easily reach the proximal end of feeding artery. However, they can also result in recanalization after embolization, and therefore should be used close to surgery. So far, there has not been any report of large number of patients treated with these agents. Denes, etc. (Horvathy et al., 2011) reported one successful CHB case embolized with ONYX before the surgery, and the patient did not experience any embolic complications. Wang et al. (2013) reported the experiences of using NBCA for the embolization of 8 cases of intracranial solid tumors with rick blood supply (including one case of CHB). One case developed intracranial hemorrhage 4 hours after preoperative embolization. They did not report the extent of occlusion achieved in these 8 cases. In this study, 33 patients underwent preoperative embolization using a liquid embolic agent and only 1 case developed intracranial hemorrhage after embolization.

In addition, only 1 patient in our study experienced postoperative ischemic stroke after complete preoperative embolization. Seven months after complete resection of the tumor, the patient developed symptoms of cerebellar infarction, which might be related to excessive preoperative embolization of the feeding artery or low perfusion pressure in surrounding normal brain tissue. Therefore, prior to the surgery we recommend cerebral angiography to verify the existing of feeding artery, and superselective angiography of the feeding artery to confirm that embolization does not reduce normal tissue blood supply, and will not damage normal tissue. Also, to avoid embolization-associated intracranial hemorrheage, surgical resection should be performed 3 days after the preoperative embolization.

Currently, although most researchers believe that preoperative embolization of CHB can reduce surgical complications and mortality, there are still a few do not agree with this view. Takeuchi (Montano et al., 2008) et al reported the treatment results from 27 cases of HB, of whom 8 underwent preoperative embolization, and found that preoperative embolization, especially partial occlusion, did not reduce the risk of surgical complications and mortality. The limitations of the study included not only small sample size and but also low level of embolization (5 patients with occlusion less than 70%). In our study, patients in experimental group had greater bleeding risk at baseline than those in the control group, and tumor size was also significantly larger (p <0.01). However, the results showed that the volume of intraoperative blood loss and transfusion were both lower in the experimental group than those in the control group (p <0.01). Furthermore, the experimental group also had significantly shorter surgery time than control group (7.6h versus 8.4h, p <0.01), and relatively lower complication rate than control group (17.4% vs 25.3%, p = 0.31), which was no statistically significant. Of the 84 cases that were successfully followed, the rate of asymptomatic recovery was slightly better in experimental group (87.1%) than that in control group (83.0%), while the rates of disability and mortality were slightly higher in the control group (9.4% and 7.5% respectively) than those in the experimental group (6.5% and 6.5% respectively). There was no statistically significant difference between 2 groups on these outcomes (p = 0.76). Therefore, we believe that preoperative embolization in patients with CHB does not increase the risk of surgical complications and mortality. Even for CHB patients with potential high risk of bleeding, preoperative embolization is reliably safe and effective.

There are a few limitations in our study. First, it is not a prospective, randomized, double-blinded trial. There was selection bias in receiving preoperative embolization, although the effect of bias might be more in favor of the control group. Second, multivariate analysis was not performed to compare the surgical and follow-up results between the experimental and control groups. For example, blood loss will certainly affect the amount of transfusion, but this was not considered when the blood transfusion was analyzed. Third, the sample size in this study is still small, relative ratio may be a better measure than percentage when presenting the risk of disability and mortality during follow-up. Fourth, this study did not include in-depth analysis of the reasons of complications, which may lead to the missing of some important information. In summary, although this study results may not represent general CHB patient population, to our best knowledge, it is still the largest retrospective cohort analysis. From the results we believe preoperative embolization is a safe and effective adjuvant therapy for CHB.

In conclusion, Preoperative embolization of CHB is a safe and effective adjuvant therapy. It can reduce the risk of intraoperative blood loss, maintain a clear surgical plane, and shorten the operational time, which may result in improved success of complete tumor resection, reduced surgical complications, postoperative morbidity and mortality.

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