Outcome and complications of endovascular embolization for vein of Galen malformations: a systematic review and meta-analysis

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OBJECT There have been many multidisciplinary approaches to the treatment of vein of Galen malformations. Endovascular embolization is the first option for treatment. However, the effects of the treatment remain controversial. The aim of this study is to assess the efficacy and safety of endovascular embolization to treat patients with vein of Galen malformations.

METHODS This paper includes a retrospective analysis of a sample of 667 patients who underwent endovascular embolization to treat vein of Galen malformations. The data were obtained through a literature search of PubMed databases. The authors also evaluate the efficacy and safety of the treatment. Mortality within the follow-up period is analyzed. Pooled estimates of proportions with corresponding 95% CIs were calculated using raw (i.e., untransformed) proportions (PRAW).

RESULTS In the 34 studies evaluated, neonates accounted for 44% of the sample (95% CI 31%–57%; $I^2 = 92.5\%$), infants accounted for 41% (95% CI 30%–51%; $I^2 = 83.3\%$), and children and adults accounted for 12% (95% CI 7%–16%; $I^2 = 52.9\%$). The meta-analysis revealed that complete occlusion was performed in 57% (95% CI 48%–65%; $I^2 = 68.2\%$) of cases, with partial occlusion in 43% (95% CI 34%–51%; $I^2 = 70.7\%$). The pooled proportion of patients showing a good outcome was 68% (95% CI 61%–76%; $I^2 = 77.8\%$), while 31% showed a poor outcome (95% CI 24%–38%; $I^2 = 75.6\%$). The proportional meta-analysis showed that postembolization mortality and complications were reported in 10% (95% CI 8%–12%; $I^2 = 42.8\%$) and 37% (95% CI 29%–45%; $I^2 = 79.1\%$), respectively. Complications included cerebral hemorrhage, cerebral ischemia, hydrocephalus, leg ischemia, and vessel perforation.

CONCLUSIONS The successful treatment of vein of Galen malformations remains a complex therapeutic challenge. The authors' analysis of clinical history and research literature suggests that vein of Galen malformations treated with endovascular embolization can result in an acceptable mortality rate, complications, and good clinical outcome. Future large-scale, multicenter, randomized trials are necessary to confirm these findings.

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KEY WORDS vein of Galen malformation; endovascular embolization; outcome; complications; meta-analysis; vascular malformations; vascular disorders

Vein of Galen aneurysmal malformations (VGAMs) are cerebral arteriovenous malformations of the choroidal system draining into the vein of Galen forerunner. Although they represent approximately 1% of all intracranial vascular lesions, they account

for 30% of vascular malformations in the pediatric age group.⁷ Endovascular embolization is the first option for VGAMs.^{15,20,30,36} The development of endovascular techniques began in the early 1980s. There have been many reports about their use in treating VGAMs since then. Given

ABBREVIATIONS DSA = digital subtraction angiography; VGAM = vein of Galen aneurysmal malformation.

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the rarity of VGAMs, most studies have been in the form of case reports. In the largest scale study of 216 patients, Lasjaunias et al.³⁶ reported a mortality rate of 10.6% overall; 74% of patients were neurologically normal on follow-up. Finally, angiographic analysis confirmed that 55% of patients achieved complete occlusion.

To date, many studies have been published on the outcome and complication rates of patients following endovascular embolization for case reports of VGAMS. However, prior to this study, no synthesis of these reviews has been reported in an overview. Therefore, in this study, we performed a meta-analysis to provide the most comprehensive evidence possible for age composition, the rate of complete occlusion, clinical outcome, and mortality and complication rates for patients treated with endovascular embolization. Our aim in this study is to help surgeons understand endovascular embolization more comprehensively.

Methods

Literature Search

A literature search was performed independently by 2 investigators using the PubMed databases. Citations for relevant English-language articles published from September 1987 through June 2014 were reviewed. For searches of the PubMed databases, we used the following combination of key words: (vein of Galen malformations OR arteriovenous aneurysms of the vein of Galen OR vein of Galen aneurysm malformations OR aneurysms of the vein of Galen) AND (endovascular embolism OR endovascular therapy). The search was limited to papers published in the English language. All relevant publications were reviewed. The references of retrieved articles were also checked for other relevant publications.

Inclusion Criteria

Cases included in our meta-analysis were required to meet all of the following criteria: 1) Only patients with vein of Galen aneurysmal malformations (VGAMs) were included and not patients with vein of Galen aneurysmal dilation. 2) Patients had undergone or were undergoing endovascular embolization, without adjuvant radiotherapy or combined surgery after the procedure. 3) Articles included in the analysis focused primarily on the outcome and complications of VGAM. Case reports with fewer than 3 treated patients were excluded.

Data Extraction

All data were independently abstracted by 2 investigators using a standardized data abstraction form. Inconsistencies were resolved by discussion and consensus. The following information was sought from each article: the first author's name, the year of publication, study country, total number of patients, age at diagnosis, treatment results, postembolization mortality rate, clinical outcome, and any major postembolization complications.

Assessment of Methodological Quality of Included Reviews

Two of the review authors (J.Y. and J.W.) independently

assessed the methodological quality of included reviews using the Cochrane Collaboration's risk of bias tool. These 2 authors rated each study for risk of bias from random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Risk of bias for each domain was rated as high (seriously weakens confidence in the results), low (unlikely to seriously alter the results), or unclear. Discrepancies were resolved through discussion. The primary analysis was repeated without studies at high risk of bias for sequence generation.

Statistical Methods

The software package R (version 3.0.2) was adopted for the statistical analysis, with the `metaprop` function, using raw (i.e., untransformed) proportions (PRAW) to calculate the pooled estimates of proportions with corresponding 95% CIs. Both the fixed-effects and the random-effects models were taken into account. We used Cochran's Q test to evaluate heterogeneity among the studies.¹⁰ An I^2 value of $< 25\%$ was defined to represent low heterogeneity, a value between 25% and 50% was defined as moderate heterogeneity, and a value $> 50\%$ was defined as high heterogeneity. The random-effects model was used if there was high heterogeneity between studies. Otherwise, the fixed-effects model was used. Funnel plots, Begg's test, and Egger's test were used to screen for potential publication bias ($p < 0.05$ was considered statistically significant).^{47,48} All p values adopted were 2-sided. The quality of the body of evidence for each outcome was judged as high, moderate, or low according to the system developed by the GRADE Working Group (<http://www.gradeworkinggroup.org/index.htm>).

Results

Identification of Eligible Studies

The literature search identified a total of 34 studies,^{3-9,12-15,17,20,22-25,28,30,32-42,45,46,50,51} which included 667 patients whose VGAMs were treated by endovascular embolization (Fig. 1). The study characteristics are shown in Tables 1 and 2.

Age at Treatment

The 667 patients from the 34 studies were divided into 3 groups according to age. The largest group included neonates (< 1 month) and accounted for 44% (95% CI 31%–57%; $I^2 = 92.5\%$) of cases. Infants (≥ 1 month to < 2 years) accounted for 41% (95% CI 30%–51%; $I^2 = 83.3\%$), and children and adults (≥ 2 years) accounted for 12% (95% CI 7%–16%; $I^2 = 52.9\%$) (Table 3).

Treatment Results

Of the 34 studies, all reported complete data regarding the extent of embolization and were included in this analysis. The complete occlusion of the lesion was initially judged by the surgeon and confirmed by digital subtraction angiography (DSA) or CT angiography scans after embolization. Complete occlusion was achieved in 57%

FIG. 1. Flowchart of review process, process of identification, and selection of studies for inclusion in the meta-analysis.

(95% CI 48%–65%; $I^2 = 68.2\%$) of cases; partial occlusion was attained in 43% (95% CI 34%–51%; $I^2 = 70.7\%$) of cases.

Number of Sessions and Postembolization Complications for Patients Who Underwent Endovascular Therapy

A total of 18 papers (164 patients) were included in the analysis (Table 4; due to a lack of data on cerebral hemorrhage and venous thrombosis, the study by Meila et al.⁴⁰ was not included in this analysis). We present the number of processes and postembolization complications for patients who underwent endovascular therapy (Table 5). As expected, patients with a completely occluded fistula, who were treated in 1 stage, had the highest incidence of complications (cerebral hemorrhage [32%] and venous thrombosis [27%]). Patients with completely occluded fistulas who were treated 2 or 3 times had considerably fewer complications (cerebral hemorrhage [21%] and venous thrombosis [24%]). Patients treated more than 3 times had the lowest incidence of complications (cerebral hemorrhage [18%] and venous thrombosis [24%]).

Follow-Up Assessment and Outcome

The follow-up period ranged from 0 to 148 months, with a mean of 63 months. The outcome score was graded on a

5-point scale according to Jones et al.,³⁰ ranging from 0 (death) to 4 (normal). A score of 1 indicates severe neurological impairment, requiring intensive supportive care. A score of 2 indicates moderate neurological impairment affecting activities of daily living and requiring significant support. A score of 3 indicates mild neurological impairment and requires little support in daily life. The developmental milestones were evaluated as well.

Clinical outcome was classified as good for scores between 4 and 3 (neurologically normal and mild developmental delays), and poor for scores of 2, 1, and 0 (moderate developmental delays, severe developmental delays, and death). However, not every study provided scores to assess grading; therefore, we classified the clinical outcome as good or poor according to the clinical symptoms of patients if a score was lacking. Patient clinical outcome was analyzed in all 34 studies. The pooled proportion of patients showing a good outcome was 68% (95% CI 61%–76%; $I^2 = 77.8\%$) (Fig. 2); a poor outcome was shown by 31% (95% CI 24%–38%; $I^2 = 75.6\%$) (Fig. 3).

Mortality

We analyzed the overall 16% mortality rate (95% CI 12%–21%; $I^2 = 59.9\%$), including the 12% mortality rate of embolized patients (95% CI 8%–16%; $I^2 = 42.8\%$) (Fig. 4) and the 47% mortality rate of nonembolized patients (95%

TABLE 1. Outcome of studies included in the meta-analysis

Authors & Year	Country	Total	Age Group at Treatment			Treatment Result		Mortality		Clinical Outcome	
			Neonate (<1 mo)	Infant (≥1 mo to <2 yrs)	Child or Adult (≥2 yrs)	Complete Occlusion	Partial Occlusion	Technical Mortality	Other	Good	Poor
Ellis et al., 2012	US	5	2	2	1	4	1	0	0	5	0
Berenstein et al., 2012	US	9	9	0	0	6	2	1	0	6	3
Meila et al., 2012	Germany	14	8	6	0	11	3	0	1	11	3
Li et al., 2011	Canada	21	7	10	4	4	17	2	2	10	11
Moon et al., 2011	Korea	5	3	2	0	1	4	2	0	3	2
Pongpech et al., 2010	Thailand	5	0	4	1	2	3	0	0	3	2
Zuccaro et al., 2010	Argentina	8	4	4	0	5	3	0	1	5	3
Heuer et al., 2010	US	11	7	3	1	7	6	1	1	8	4
Hassan et al., 2010	Egypt	8	0	5	3	6	1	0	0	7	1
McSweeney et al., 2010	England	28	21	3	4	11	17	1	1	20	8
Lasjaunias et al., 2006	France	216	23	153	40	119	97	3	20	173	43
Gupta et al., 2006	India	15	0	6	9	13	2	0	0	15	0
Wong et al., 2006	Australia	9	9	0	0	5	4	1	2	4	5
Fullerton et al., 2003	US	27	21	5	1	21	6	0	4	23	4
Jones et al., 2002	US	13	8	4	1	NA	NA	1	4	7	6
Chevret et al., 2002	France	18	18	0	0	NA	NA	0	6	10	8
Frawley et al., 2002	Australia	9	9	0	0	NA	NA	0	3	6	3
Komiyama et al., 2001	Japan	6	3	1	0	NA	NA	1	2	1	3
Mitchell et al., 2001	Australia	5	4	1	0	3	2	1	1	3	2
Campi et al., 1998	France	3	2	1	0	2	1	1	0	2	1
Halbach et al., 1998	US	8	2	6	0	4	4	0	0	8	0
Iizuka et al., 1998	Japan	3	2	1	0	NA	NA	0	2	1	2
Borthne et al., 1997	Norway	14	5	5	4	NA	NA	1	3	10	4
Lasjaunias et al., 1995	France	52	31	16	5	NA	NA	3	10	31	21
Rodesch et al., 1994	France	12	0	12	0	8	4	0	0	8	4
Lylyk et al., 1993	US	28	11	13	4	13	15	3	2	17	11
Friedman et al., 1993	US	11	11	0	0	NA	NA	0	0	8	3
Lasjaunias et al., 1991	Canada	34	13	14	7	16	18	1	1	18	16
Garcia-Monaco et al., 1991	France	22	19	7	4	16	6	2	0	20	2
Casasco et al., 1991	Argentina	7	1	5	1	5	2	1	0	7	0
Ciricillo et al., 1990	US	8	8	0	0	NA	NA	1	1	2	6
Lasjaunias et al., 1989	France	15	NA	NA	NA	10	5	0	2	4	11
Hanner et al., 1988	US	15	NA	NA	NA	6	8	1	2	12	3
Burrows et al., 1987	Canada	3	1	1	1	0	3	1	0	1	2

NA = not available.

CI 24%–69%; $I^2 = 90.7\%$). At the same time, we analyzed the causes of death with the embolized patients, including the technical reasons related to embolization (2% [95% CI 1%–3%], $I^2 = 0\%$), such as cerebral hemorrhage, broken catheter, catheter perforation, intractable congestive heart failure due to failed embolization, and other causes (comorbidities) (6% [95% CI 4%–8%], $I^2 = 33.7\%$), such as persistent heart failure, subdural hematoma, pulmonary infarct, progressive neurological deterioration, rejected treatment, melting brain syndrome, severe seizures, and multiple organ failure (Table 6).

Postembolization Complications

The analysis included the following postembolization complications: cerebral hematoma, cerebral ischemia, macrocephaly or hydrocephalus, mental retardation or developmental delay, leg ischemia, and vessel perforation. The proportional meta-analysis showed a pooled proportion of 37% (95% CI 29%–45%; $I^2 = 79.1\%$) (Fig. 5).

Cerebral hemorrhage was reported most frequently as a postembolization complication. Cerebral hemorrhage data were available for all studies. The proportional meta-analysis showed that a pooled proportion of 5% (95% CI

TABLE 2. Complications in studies included in the meta-analysis

Authors & Year	Country	Total	Complications	Cerebral Hemorrhage	Cerebral Ischemia	Hydroceph	Developmental Delay	Leg Ischemia	Vessel Perforation	FU (mos)
Ellis et al., 2012	US	5	3	2	1	0	NA	0	0	2–97
Berenstein et al., 2012	US	9	4	4	3	0	NA	1	1	NA
Meila et al., 2012	Germany	14	4	2	0	0	NA	0	4	1–148
Li et al., 2011	Canada	21	11	1	0	4	7	0	NA	1–24
Moon et al., 2011	Korea	5	2	2	0	0	0	NA	NA	0–72
Pongpech et al., 2010	Thailand	5	2	0	1	0	NA	0	2	12–108
Zuccaro et al., 2010	Argentina	8	1	1	0	1	NA	0	0	NA
Heuer et al., 2010	US	11	4	3	1	0	NA	0	0	0–144
Hassan et al., 2010	Egypt	8	1	0	0	0	NA	1	0	NA
McSweeney et al., 2010	England	28	10	3	8	6	NA	2	3	0–60
Lasjaunias et al., 2006	France	216	21	11	0	0	13	8	7	0–12
Gupta et al., 2006	India	15	6	2	1	0	1	1	0	1–12
Wong et al., 2006	Australia	9	5	1	4	0	1	NA	0	0–60
Fullerton et al., 2003	US	27	13	0	0	0	9	3	NA	0–54
Jones et al., 2002	US	13	6	3	NA	6	NA	2	NA	3–108
Chevret et al., 2002	France	18	9	NA	NA	NA	9	NA	NA	63
Frawley et al., 2002	Australia	9	4	0	3	0	1	NA	NA	1–48
Komiyama et al., 2001	Japanese	6	2	1	0	0	0	0	1	6–144
Mitchell et al., 2001	Australia	5	0	0	0	0	0	0	NA	0–29
Campi et al., 1998	France	3	1	1	NA	1	1	2	NA	13–39
Halbach et al., 1998	US	8	2	2	0	2	1	0	NA	3–105
Iizuka et al., 1998	Japanese	3	2	0	0	0	2	NA	NA	5
Borthne et al., 1997	Norway	14	8	0	2	7	NA	1	NA	1–72
Lasjaunias et al., 1995	France	52	21	3	4	0	11	3	NA	120
Rodesch et al., 1994	France	12	4	0	0	2	4	2	NA	6
Lylyk et al., 1993	US	28	11	3	2	4	4	0	2	12–24
Friedman et al., 1993	US	11	3	2	6	4	3	0	NA	1–30
Lasjaunias et al., 1991	Canada	34	21	2	NA	1	3	1	NA	6–24
Garcia-Monaco et al., 1991	France	22	3	2	0	0	0	NA	NA	6
Casasco et al., 1991	Argentina	7	0	0	0	0	0	0	1	4–23
Ciricillo et al., 1990	US	8	6	2	5	1	3	0	1	7–62
Lasjaunias et al., 1989	France	15	8	3	3	2	1	NA	0	NA
Hanner et al., 1988	US	15	5	1	2	1	0	NA	0	NA
Burrows et al., 1987	Canada	3	2	1	1	0	NA	0	NA	7–72

FU = follow-up; Hydroceph = hydrocephalus.

4%–7%; $I^2 = 16.4\%$) of included patients suffered a cerebral hemorrhage. Of the 34 studies examined, 30 reported complete data regarding cerebral ischemia and were subsequently included in this analysis. The rate of cerebral ischemia in these studies was 6% (95% CI 3%–10%; $I^2 = 60.8\%$). Hydrocephalus was analyzed in 33 of the 34 studies. The pooled proportion of hydrocephalus was 0% (95% CI 0%–1%; $I^2 = 47.7\%$). Developmental delay was analyzed in 23 of the 34 studies. The pooled proportion of developmental delay was 12% (95% CI 8%–17%; $I^2 = 64.2\%$). Leg ischemia was analyzed in 26 of the 34 studies. The pooled proportion of leg ischemia was 3% (95%

CI 2%–5%; $I^2 = 0\%$). Vessel perforation was analyzed in 17 of the 34 studies. The pooled proportion of vessel perforation was 3% (95% CI 1%–5%; $I^2 = 0\%$).

Main Outcome Criteria (Mortality, Good/Poor Clinical Outcome, Complications) Over the 1980s, 1990s, and 2000s

There were 34 papers included in this analysis. Main outcomes were, first, the mortality rate of embolized patients during the 1980s, 1990s, and 2000s were 17%, 12%, and 12%, respectively. Second, the complication rate of embolized patients over the 1980s, 1990s, and 2000s were 45%, 38%, and 35%, respectively. Third, the good clinical

TABLE 3. Meta-analysis of the outcome and complications of endovascular embolization for vein of Galen malformations

Variable	No. of Events	Total	Proportion (95% CI)	Model	Test of Heterogeneity*		p Publication Bias		Quality of Evidence (GRADE)
					I ²	p Value	Egger's Test†	Begg's Test‡	
Age at treatment									
Neonate (<1 mo)	198	561	44% (31–57%)	R	92.5%	<0.0001	0.003829	0.9069	Very low
Infant (≥1 mo to <2 yrs)	278	561	41% (30–51%)	R	83.3%	<0.0001	0.1051	0.1819	Moderate
Child or adult (≥2 yrs)	91	561	12% (7–16%)	R	52.9%	0.0011	0.6705	0.1671	Moderate
Treatment result									
Complete occlusion	298	533	57% (48–65%)	R	68.2%	<0.0001	0.9470	0.6072	Moderate
Partial occlusion	234	533	43% (34–51%)	R	70.7%	<0.0001	0.9327	0.674	Moderate
Clinical outcome									
Good	469	667	68% (61–76%)	R	77.8%	<0.0001	0.001599	0.01427	Very low
Poor	197	667	31% (24–38%)	R	75.6%	<0.0001	0.001756	0.03252	Very low
Overall mortality	136	775	16% (12–21%)	R	59.9%	<0.0001	0.0002953	0.02227	Very low
Nonembolized patients	36	101	47% (24–69%)	R	90.7%	<0.0001	0.1659	0.5507	Moderate
Embolized patients	99	667	10% (8–12%)	F	42.8%	0.005	0.002346	0.0007542	Very low
Technical mortality	29	667	2% (1–3%)	F	0%	0.9163	0.0002155	1e-04	Very low
Other reasons	71	667	6% (4–8%)	F	33.7%	0.0306	0.03837	0.001484	Very low
Complications	205	667	37% (29–45%)	R	79.1%	<0.0001	3.467e-06	0.7892	Low
Cerebral hemorrhage	58	649	5% (4–7%)	F	16.4%	0.2062	0.0001468	7.628e-05	Very low
Cerebral ischemia	47	599	6% (3–10%)	R	60.8%	<0.0001	3.196e-05	4.939e-05	Very low
Hydrocephalus	42	649	0% (0–1%)	F	47.7%	0.0014	0.00017	9.377e-06	Very low
Developmental delay	74	549	12% (8–17%)	R	64.2%	<0.0001	0.004516	0.007496	Very low
Leg ischemia	27	571	3% (2–5%)	F	0%	0.8258	0.2076	0.02689	Moderate
Vessel perforate	22	407	3% (1–5%)	F	0%	0.5393	0.1073	0.001202	Moderate

F = fixed-effects model; R = random-effects model.

* $p < 0.10$ is considered statistically significant for Q statistics; I^2 is interpreted as the proportion of total variation contributed by between-study variation.† Egger's test to evaluate publication bias, $p < 0.05$ is considered statistically significant.‡ Begg's test to evaluate publication bias, $p < 0.05$ is considered statistically significant.

outcome rate of embolized patients over the 1980s, 1990s, and 2000s was 49%, 70%, and 70%, respectively, whereas the poor clinical outcome rate of embolized patients over the 1980s, 1990s, and 2000s was 51%, 30%, and 28%, respectively (Table 7).

Methodological Quality of Included Reviews

The quality of the 34 studies retained for analysis can be found in the text of the present paper. It shows the risk of bias ratings for each trial. Twenty-seven trials were at high risk of bias for sequence generation, and these included 433 participants. Twelve studies were at high risk of bias because of inadequate allocation concealment, and 22 were unclear. Lack of blinding of assessors created a high risk of bias in 29 studies, but it was unclear if assessors were blinded in 5 trials. Seventeen studies were at high risk of bias for failing to blind project staff, and 17 trials were unclear on this issue. At the trial level, only one was at high risk of bias for missing data and one was unclear, but the complete outcome data were described in 32 trials, though missing data for the primary outcome was not a concern. Nineteen studies seemed to be completely free from selective outcome reporting (low risk of bias). Thirteen studies were not completely free from selective

outcome reporting (high risk of bias). It was unclear if 2 trials reported all outcomes, but the primary outcome was known for almost all participants in the review. To test for bias, the primary analysis was repeated without studies at high risk of bias for sequence generation (Figs. 6 and 7).

Grade of Evidence

The quality of the evidence was rated as moderate for 7, low for 1, and very low for 11. Risk of bias and publication bias introduced by study design was the reason for downgrading the quality from high to very low, with the absence of blinding of outcome assessors being the most serious potentially avoidable concern.

Heterogeneity

As is shown, there was significant statistical heterogeneity for age at diagnosis: neonates ($p < 0.0001$, $I^2 = 92.5\%$); infant ($p < 0.0001$, $I^2 = 83.3\%$); and children and adults ($p = 0.0011$, $I^2 = 52.9\%$). In the treatment results, heterogeneity was calculated as complete occlusion ($p < 0.0001$, $I^2 = 68.2\%$) and partial occlusion ($p < 0.0001$, $I^2 = 70.7\%$). In terms of clinical outcome, the results were good clinical outcome ($p < 0.0001$, $I^2 = 77.8\%$) and poor clinical outcome ($p < 0.0001$, $I^2 = 75.6\%$). In the heterogeneity for

TABLE 4. Number of sessions and postembolization complications of included studies

Authors & Year	Country	Total	1 Session			2–3 Sessions			>3 Sessions		
			No. of Patients	CH	VT	No. of Patients	CH	VT	No. of Patients	CH	VT
Ellis et al., 2012	US	5	1	1	0	4	1	1	0	0	0
Berenstein et al., 2012	US	9	1	1	0	3	1	0	5	2	1
Meila et al., 2012	Germany	14	1	NA	NA	6	NA	NA	7	NA	NA
Li et al., 2011	Canada	21	NA	NA	NA	NA	NA	NA	NA	NA	NA
Moon et al., 2011	Korea	5	1	0	0	2	1	0	2	1	0
Pongpech et al., 2010	Thailand	5	3	1	1	0	0	0	2	0	1
Zuccaro et al., 2010	Argentina	8	1	0	0	7	2	0	0	0	0
Heuer et al., 2010	US	13	6	2	2	5	2	1	0	0	0
Hassan et al., 2010	Egypt	8	7	1	2	1	0	0	0	0	0
McSweeney et al., 2010	England	28	9	3	3	12	4	6	7	1	2
Lasjaunias et al., 2006	France	216	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gupta et al., 2006	India	15	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wong et al., 2006	Australia	9	2	1	1	5	1	2	1	0	1
Fullerton et al., 2003	US	27	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jones et al., 2002	US	13	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chevret et al., 2002	France	18	NA	NA	NA	NA	NA	NA	NA	NA	NA
Frawley et al., 2002	Australia	9	2	1	1	4	0	0	3	1	1
Komiyama et al., 2001	Japan	6	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mitchell et al., 2001	Australia	5	1	1	0	3	0	1	1	0	0
Campi et al., 1998	France	3	NA	NA	NA	NA	NA	NA	NA	NA	NA
Halbach et al., 1998	US	8	5	2	2	3	0	0	0	0	0
Iizuka et al., 1998	Japan	3	NA	NA	NA	NA	NA	NA	NA	NA	NA
Borthne et al., 1997	Norway	14	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lasjaunias et al., 1995	France	52	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rodesch et al., 1994	France	12	5	1	2	4	0	1	3	0	1
Lylyk et al., 1993	US	28	NA	NA	NA	NA	NA	NA	NA	NA	NA
Friedman et al., 1993	US	11	3	1	0	7	1	2	NA	0	0
Lasjaunias et al., 1991	Canada	34	NA	NA	NA	NA	NA	NA	NA	NA	NA
Garcia-Monaco et al., 1991	France	22	NA	NA	NA	NA	NA	NA	NA	NA	NA
Casasco et al., 1991	Argentina	7	2	0	0	4	0	0	1	0	0
Ciricillo et al., 1990	US	8	1	0	0	3	1	2	4	1	1
Lasjaunias et al., 1989	France	15	5	2	1	6	0	1	4	0	0
Hanner et al., 1988	US	15	NA	NA	NA	NA	NA	NA	NA	NA	NA
Burrows et al., 1987	Canada	3	1	0	0	2	2	1	0	0	0

CH = cerebral hemorrhage; VT = venous thrombosis.

mortality, there was significant statistical heterogeneity for overall mortality rate ($p < 0.0001$, $I^2 = 59.9\%$) and mortality for the nonembolized patients ($p < 0.0001$, $I^2 = 90.7\%$); however, there was not significant statistical heterogeneity for mortality for embolized patients ($p = 0.005$, $I^2 = 42.8\%$), technical mortality ($p = 0.9163$, $I^2 = 0\%$), and other reasons ($p = 0.0306$, $I^2 = 33.7\%$). There was also significant heterogeneity for postembolization complications ($p < 0.0001$, $I^2 = 79.1\%$): cerebral ischemia ($p < 0.0001$, $I^2 = 60.8\%$) and developmental delay ($p < 0.0001$, $I^2 = 64.2\%$), with the exception of cerebral hemorrhage ($p = 0.2062$, $I^2 = 16.4\%$), hydrocephalus ($p = 0.0014$, $I^2 = 47.7\%$), leg ischemia ($p = 0.8258$, $I^2 = 0\%$), and vessel perforation ($p = 0.5393$, $I^2 = 0\%$).

TABLE 5. Number of sessions and postembolization complications for patients who underwent endovascular therapy

No. of Sessions	Total No. of Patients	Postembolization Complications	
		CH*	VT
1	56	18 (32%)	15 (27%)
2–3	75	16 (21%)	18 (24%)
>3	33	6 (18%)	8 (24%)
Total	164	40 (24%)	41 (25%)

* Cerebral hemorrhage includes parenchymal bleeding, intraventricular hemorrhage, and subarachnoid hemorrhage.

FIG. 2. Estimates of the proportion of the good outcome, including the 95% CI from the random-effects model and the number of patients for each study. W = weighted.

Statistical heterogeneity suggests that there might be differences in the effects of endovascular treatment for VGAMs across settings and populations, and we conducted prespecified subgroup analyses for all analyses according to race, the period, and the quality of profile. Trials were conducted in 13 countries. As described above (Fig. 8), endovascular treatment for VGAMs was associated with significant reductions in mortality, complications, and clinical outcome in both Asia and Africa. Trials were also conducted over the 1980s, 1990s, and 2000s. Endovascular treatment for VGAMs was associated with significant reductions in mortality, complications, and clinical outcome in both the 1990s and 2000s, while the difference

between subgroups for the outcome was not significant. A nonrepresentative subset of studies reported data by quality of profile (Fig. 9), but these comparisons cannot be interpreted meaningfully.

Publication Bias

Begg's test and Egger's test showed no evidence of publication bias in some variables evaluated, such as age at treatment (infant, child, or adult), treatment result, mortality for the nonembolized patients, and complications (leg ischemia, vessel perforation) ($p > 0.05$). However, publication bias was identified in the following areas: age at treatment (neonate), clinical outcome, mortality (total

FIG. 3. Estimates of the proportion of the poor outcome, including the 95% CI from the random-effects model and the number of patients for each study.

mortality, mortality for the embolized patients, technical mortality, other reasons), and complications (cerebral hemorrhage, cerebral ischemia, hydrocephalus, and developmental delay) ($p < 0.05$).

Discussion

Vein of Galen aneurysmal malformations are arteriovenous malformations of the choroidal system that develop in the early embryonic stage.¹ They represent 30% of vascular malformations in the pediatric age group.

Routine prenatal ultrasound screening has become more and more common. All patients in this review were evaluated with imaging studies, such as MRI and CT. The

diagnosis can be confirmed by vascular studies, such as MR angiography, CT angiography, or DSA. However, the therapeutic method was classified into 4 groups, including endovascular therapy, microsurgery (craniotomy and clip occlusion of the vessel), Gamma Knife surgery, and conservative management. As is well known, endovascular treatment has long been accepted as the first option for the treatment VGAMs.^{15,20,30,36,49} High mortality and morbidity of microsurgery, exceeding 90% in some studies, has led to the development of endovascular techniques that more effectively and safely treat VGAMs.^{2,26,29,43} However, Gamma Knife surgery achieved favorable outcomes in 88.9% of cases for long-term effects, as reported by Payne

FIG. 4. Estimates of the postembolization mortality rate, including the 95% CI from the fixed-effects model and the number of patients for each study.

et al.⁴⁴ Finally, patients who refused both endovascular and microsurgical treatment, choosing conservative medical management, had a high mortality rate.

Endovascular embolization has been more and more widely applied in clinics in recent years.^{3,12,40} The results suggest that advances in endovascular treatment have greatly improved the outcome of patients with VGAMs. However, what is the outcome for endovascular treatment? What are complication rates for VGAMs? No studies have looked at this aspect of the systematic evaluation before. The purpose of our study was to assess the outcome and complications of endovascular embolization to gain a better understanding of endovascular management.

Age at Treatment

When assessing the efficacy of endovascular embolization, the surgeon must often consider the age factor. Age is the main determinant of mortality risk. Accordingly, our study looks at the constituent ratio of patient age groups after endovascular embolization. In fact, it is a simple matter of constituent ratio. To some extent, the constituent ratio marks the distribution of age for the best treatment period and the prelude for the outcome of disease with embolization intervention, when compared with 100% natural history mortality rate of VGAMs.¹⁹ On the other hand, constituent ratios of each age group have been affected by different factors or initial presentations,

TABLE 6. Causes of mortality in patients who underwent embolization

Authors & Year	Country	Technical Reasons					Other (comorbidities)									
		Total	CH	BC	CP	ICHF*	Total	PHF	SDH	PI	PND	RT	MBS	SS	MOF	
Ellis et al., 2012	US	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Berenstein et al., 2012	US	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
Meila et al., 2012	Germany	0	0	0	0	0	1	NA	NA	NA	NA	NA	NA	NA	NA	
Li et al., 2011	Canada	0	0	0	0	0	6	4	0	0	2	0	0	0	0	
Moon et al., 2011	Korea	2	2	0	0	0	0	0	0	0	0	0	0	0	0	
Pongpech et al., 2010	Thailand	0	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	
Zuccaro et al., 2010	Argentina	0	0	0	0	0	1	1	0	0	0	0	0	0	0	
Heuer et al., 2010	US	1	1	0	0	0	1	1	0	0	0	0	0	0	0	
Hassan et al., 2010	Egypt	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
McSweeney et al., 2010	England	1	1	0	0	0	1	0	0	0	0	0	0	0	1	
Lasjaunias et al., 2006	France	3	NA	NA	NA	NA	20	NA	NA	NA	NA	NA	NA	NA	NA	
Gupta et al., 2006	India	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Wong et al., 2006	Australia	1	NA	NA	NA	NA	2	0	0	0	2	0	0	0	0	
Fullerton et al., 2003	US	0		0	0	0	4	4	0	0	0	0	0	0	0	
Jones et al., 2002	US	1	1	0	0	0	4	0	0	0	1	0	0	0	3	
Chevret et al., 2002	France	0	0	0	0	0	6	6	0	0	0	0	0	0	0	
Frawley et al., 2002	Australia	0	0	0	0	0	3	1	0	0	0	0	2	0	0	
Komiyama et al., 2001	Japan	1	0	0	1	0	2	1	1	0	0	0	0	0	0	
Mitchell et al., 2001	Australia	1	0	0	0	1	1	0	0	0	0	0	0	1	0	
Campi et al., 1998	France	1	1	0	0	0	0	0	0	0	0	0	0	0	0	
Halbach et al., 1998	US	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Iizuka et al., 1998	Japan	0	0	0	0	0	2	0	0	0	0	0	2	0	0	
Borthne et al., 1997	Norway	1	1	0	0	0	3	2	0	1	0	0	0	0	0	
Lasjaunias et al., 1995	France	2	2	0	0	0	1	0	0	0	0	1	0	0	0	
Rodesch et al., 1994	France	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Lylyk et al., 1993	US	5	0	0	2	1	2	1	0	0	1	0	0	0	0	
Friedman et al., 1993	US	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Lasjaunias et al., 1991	Canada	1	1	0	0	0	1	0	1	0	0	0	0	0	0	
Garcia-Monaco et al., 1991	France	2	2	0	0	0	0	0	0	0	0	0	0	0	0	
Casasco et al., 1991	Argentina	1	0	0	1	0	0	0	0	0	0	0	0	0	0	
Ciricillo et al., 1990	US	1	0	1	0	0	1	0	0	1	0	0	0	0	0	
Lasjaunias et al., 1989	France	0	0	0	0	0	2	0	2	0	0	0	0	0	0	
Hanner et al., 1988	US	1	1	0	0	0	2	2	0	0	0	0	0	0	0	
Burrows et al., 1987	Canada	1	1	0	0	0	0	0	0	0	0	0	0	0	0	

BC = broken catheter; CH = cerebral hemorrhage; CP = catheter perforation; ICHF = intractable congestive heart failure; MBS = melting brain syndrome; MOF = multiple organ failure; PHF = persistent heart failure; PI = pulmonary infarct; PND = progressive neurological deterioration; RT = rejected treatment; SDH = subdural hematoma; SS = severe seizures.

* Due to failed embolization.

reflecting the characteristics of the diseases at different stages.

First, the result of our constituent ratio shows that the neonate group accounts for the highest percentage of cases at 44% (95% CI 31%–57%). As congestive heart failure cannot be controlled effectively with medical treatment, most patients cannot wait until they are 5 or 6 months of age when emergency embolization is suggested.³⁶ Severe cardiorespiratory alterations are the most significant symptoms associated with neonatal diagnosis. Cardiovascular and respiratory distress syndromes result from the

high-flow arteriovenous shunts of VGAM.¹⁶ Indeed, high-output cardiac failure was presented in 94% of VGAM cases in the neonatal period, as reported by Rodesch et al.⁴⁶ Roughly, the higher the constituent ratio of neonate group with embolization, the greater the proportion of emergency treatments.

The next age group, the infant group, accounts for 41% (95% CI 30%–51%). Whereas congestive heart failure can be managed with medical treatment or is not present, endovascular embolization should be deferred until the best time for the operation. Smaller shunts and milder cardiac

FIG. 5. Estimates of the rate of postembolization complications, including the 95% CI from the random-effects model and the number of patients for each study.

symptoms are the most common symptoms for infants. Hydrocephalus is the most important symptom associated with a diagnosis of VGAM during infancy. Communicating hydrocephalus is considered to be a result of an impaired CSF resorption function of arachnoid granulations by subarachnoid blood, whereas noncommunicating hydrocephalus results from a venous aneurysm oppressing the corpora quadrigemina or aqueduct, leading to blockage of cerebrospinal fluid circulation.¹⁶ Other clinical presentations associated with diagnosis during infancy were seizures and increased head circumference. The clinical symptoms of this period often did not need immediate treatment. So, to some extent, the rate of elective emboli-

zation procedures was reflected by the constituent ratio of infant group.

Finally, the group with children and adults accounts for the lowest percentage at 12% (95% CI 7%–16%). The symptoms of this group are often milder. Headaches and subarachnoid hemorrhage are the most typical symptoms for children. In these cases, lesions are generally small and the arteriovenous shunts have low velocity. Adults are rarely diagnosed with VGAM, accounting for the low constituent ratio in children and adults who have undergone embolization, but diagnosis in this group is becoming more common as imaging techniques are improving.¹⁶ This shows that our understanding of VGAMs is still pro-

TABLE 7. Main outcome criteria (mortality, good/poor clinical outcome, complications) over the 1980s, 1990s, and 2000s

Decade	Mortality of Embolized Patients	Complications	Clinical Outcome	
			Good	Poor
1980s	17% (4–30%)	45% (29–62%)	49% (8–89%)	51% (11–92%)
1990s	12% (5–18%)	38% (24–52%)	70% (57–83%)	30% (17–43%)
2000s	12% (7–17%)	35% (24–45%)	70% (61–79%)	28% (20–36%)

gressing. Lesions producing mild symptoms or asymptomatic lesions are not dangerous.

The distribution of constituent ratio of the age groups reflected the choice of timing for endovascular treatment. Lasjaunias et al.³⁶ recommended that the timing of endovascular treatment should be determined by the clinical presentation of the patient. Treatment should be delayed until the patient is 5 or 6 months of age, because it presents little risk to normal brain maturation and maximizes the efficacy of treatment.²¹ As soon as the cardiovascular or neurological symptoms cannot be managed medically, emergency embolization should be performed.

Treatment Results

Complete occlusion and partial occlusion were performed in 57% (95% CI 48%–65%) and 43% (95% CI 34%–51%) of cases, respectively; the proportion was almost 50%/50%. Endovascular embolization can occlude the lesion entirely; however, complete occlusion performed in a single session is extremely dangerous. Some authors believe that the advantage of partial occlusion lies in reducing the risk of congestive heart failure in neonates, and, in some centers, the outcome of partial occlusion may be superior to that of complete occlusion.⁹ Partial occlusion may itself promote thrombosis in lesions and avoid the later procedures. In fact, staged embolization has been carried out in many patients with larger lesions. The above opinions are consistent with our statistical results. Here the goal is not complete occlusion of the lesion, but rather partial obliteration, to redistribute blood flow to allow for normal cardiac and neurological development.²⁰ As a result, with very similar statistical re-

sults, we can draw the conclusion that a decision whether to adopt the method of complete occlusion depends not only on the type of lesion, the amount of blood supplying arteries and venous drainage, but also, and more importantly, on the experience of the surgeon. From the perspective of the long-term results, however, we must clarify that the ultimate goal of treatment after the conclusion of the staged procedures was complete occlusion to avoid recruitment and expansion with time. The purpose of the partial occlusion is only to gain time and to control the acute situation.

Clinical Outcome

Clinical outcome is one of the important indicators of effective embolization therapy. In our study, of the 667 patients who underwent endovascular embolization between 1987 and 2014, 68% had a good outcome and 31% had a poor outcome, including 10% who died. In the literature review by Khullar et al.,³¹ of the 337 patients who underwent endovascular embolization between 2001 and 2010, 60.8% had a good outcome, 39.1% had a poor outcome, and 15.7% died. Comparing these 2 studies, the poor outcome and mortality rates were lower in the former study than the latter. The reason for the difference is due to different inclusion criteria and the number of case studies analyzed. In other words, our research had looser inclusion criteria and included more case studies.

The good/poor clinical outcome was not only related to embolization technology, but also to a number of other factors, such as poor clinical presentation with multiorgan failure, the presence of neurological deficit, CT or MRI findings of parenchymal calcifications and extensive en-

FIG. 6. Risk of bias graph. Review of our judgment about each risk of bias item presented as percentages across all included studies. Figure is available in color online only.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Berenstein 2012	?	?	+	?	+	+	+
Borthne 1997	?	?	+	?	+	+	+
Burrows 1987	?	?	+	+	+	?	?
Campi 1998	+	?	+	?	+	+	?
Casasco 1991	?	?	+	?	+	+	?
Chevet 2002	?	?	+	?	+	+	+
Ciricillo 1990	?	?	+	?	+	+	?
Ellis 2012	?	?	+	+	+	+	?
Frawley 2002	+	?	+	+	+	+	?
Friedman 1993	+	?	+	?	+	+	?
Fullerton 2003	+	?	+	?	+	+	+
Garcia-Monaco 1991	+	?	?	?	+	+	?
Gupta 2006	+	+	+	+	+	+	?
Halbach 1998	+	?	+	+	+	+	?
Hanner 1988	+	?	+	?	+	+	?
Hassan 2010	+	?	+	+	+	+	?
Heuer 2010	+	?	+	+	+	+	?
Iizuka 1998	+	+	?	?	+	+	+
Jones 2002	+	+	?	?	+	+	+
Komiyama 2001	+	+	?	?	+	+	?
Lasjaunias 1989	+	?	+	?	+	+	?
Lasjaunias 1991	+	?	+	?	+	+	?
Lasjaunias 1995	+	?	+	+	+	+	?
Lasjaunias 2006	+	?	+	?	?	?	?
Li 2011	+	+	+	+	+	+	?
Lylyk 1993	+	?	+	+	+	+	+
McSweeney 2010	+	+	+	+	+	+	+
Meila 2012	+	?	+	+	+	+	+
Mitchell 2001	+	+	+	+	+	+	?
Moon 2011	+	+	+	+	+	+	+
Pongpech 2010	+	+	+	+	+	+	?
Rodesch 1994	+	+	+	+	+	+	?
Wong 2006	+	+	?	?	+	+	?
Zuccaro 2010	+	+	+	+	+	+	?

FIG. 7. Assessment of risk of bias in studies on effect of prognosis and postembolization complications after endovascular embolization for vein of Galen malformations. Red circles (−) indicate a high risk of bias, yellow circles (?) indicate an unclear risk of bias, and green circles (+) indicate a low risk of bias. Figure is available in color online only.

cephalomalacic parenchymal changes, DSA findings of arterial steal, and evidence of high-flow multifeeder shunts.¹⁸ Emergency embolization should be performed in patients with severe congestive heart failure, progressive occlusion of the venous outflow, and the existence of artery steal, but not if there is evidence of permanent brain damage on MRI or CT scans. In a word, in deciding how to treat a VGAM patient, we should consider all the above factors to improve the outcome for patients.

Mortality

The overall mortality rate in this study was 16%. Mortality for embolized patients (10%) was lower than that for nonembolized patients (47%). However, the nonembolized patient group included patients who did not receive endovascular embolization, but could have received other treatments such as microsurgery, Gamma Knife surgery, or medical management. Therefore, to some extent, we can draw a conclusion that endovascular embolization is the first treatment option for VGAMs in comparison with microsurgery, Gamma Knife surgery, or medical management. This result is in accord with the conclusion of Khullar and colleagues' study.³¹ We further analyzed the causes of death in embolized patients. Mortality related to embolization process techniques (2%) was lower than mortality due to other causes or comorbidities (6%). To some extent, the results proved the safety of embolization. On further analysis, the technical complications, in order of high to low incidence, were cerebral hemorrhage, intractable congestive heart failure due to failed embolization, broken catheter, and catheter perforation.

Complications

Cerebral Hemorrhage and Cerebral Ischemia

The rates of postembolization complications are described in *Results*. From the results shown, we can draw the following conclusion. If we completely occlude the fistula or occlude most fistulas at one time, the chances of complications with cerebral hemorrhage and cerebral ischemia are higher. The key aim of endovascular therapy of VGAM is to occlude the arteriovenous fistula and try to avoid damaging the venous drainage system.²⁷ Given the deep lesion site, complex structure, and difficult surgery, such factors are likely to cause cerebral hemorrhage, even leading to death. This is due to a sudden reversal of blood steal resulting in excessive blood perfusion syndrome. After occluding the main blood artery supply of the VGAM, the internal pressure of lesions and blood flow velocity are significantly lower. The blood in the lesions is blocked, leading to thrombosis. Blood clots are extended to the collateral venous circulation, which connects with the VGAM. These veins are often the most important routes of normal brain tissue drainage. Extended blood clots can cause adverse consequences.¹¹

The results of our study prove the existence of a relationship between the number of processes and the extent of postembolization complications. It is ideal to achieve complete occlusion of the lesion in the fewest number of sessions possible, but endovascular embolization often requires multiple sessions. The number of sessions is deter-

FIG. 8. The subgroup analyses for rate of postembolization complications according to race, including the 95% CI from the random-effects model and the number of patients for each study.

mined by the angioarchitecture of the lesion and the clinical presentation of the patient. Endovascular embolization is usually performed at 3- to 6-month intervals.³⁶ Intracerebral hemorrhage and venous thrombosis can be largely avoided by staging the embolization procedure.¹⁶

Hydrocephalus and Developmental Delay

As a matter of fact, hydrocephalus and developmental

delay are not in themselves complications of embolization treatments for VGAM, but both frequently impact on the outcome of VGAM patients. The pathological mechanism is as follows. The vein of Galen extends to the size of a tennis ball, oppressing the corpora quadrigemina and aqueduct. This leads to the blockage of cerebrospinal fluid circulation, namely hydrocephalus; a blood steal then triggers cerebral ischemia and encephalatrophy, eventually leading

FIG. 9. The subgroup analyses for rate of postembolization complications according to the quality of profile, including the 95% CI from the random-effects model and the number of patients for each study.

to developmental delay, mental retardation, or neurological deficit.

Geibprasert et al.¹⁸ believed that proper early management by decreasing the venous pressure through embolization of the high-flow shunt improves the chance for a better outcome in these patients. In these cases, early ventricular shunting is known to have a poor outcome.²¹ Therefore, ventricular drainage should be used only for those patients who do not improve after embolization or who have hydrocephalus unrelated to the VGAM. The same applies to patients with mental retardation.

Leg Ischemia and Vessel Perforation

In comparison with adults, leg ischemia and vessel

perforation are characteristic complications for pediatric patients with femoral artery occlusion, due to repeated femoral artery puncture. We must be very careful in terms of compression and hemostasis after the procedure to prevent compromising the long-term patency of the vessels. Another technical complication of vessel perforation or microcatheter rupture can result in stroke and the permanent neurological deficit of mild hemiparesis where perforation of the feeding arteries occurred during the operation. Immediate embolization with *N*-butyl cyanoacrylate or Onyx should be performed. Perforation of the venous sac has been reported to occur during positioning of the microcatheter during coil embolization and can usually be managed by reversal of anticoagulation and continuation

of coil embolization. Leg ischemia and vessel perforation belong to the category of technical complications. These complications can be avoided by surgical proficiency and careful manipulation. Potential complications include pulmonary embolization. Pulmonary embolization with embolic agents is common, considering the high flow across the intracranial shunt.

Main Outcome Criteria (Mortality, Good/Poor Outcome, Complications) Over the 1980s, 1990s, and 2000s

Our literature review extended over several decades. Most studies actually included in the analysis were from the 1980s, 1990s, and 2000s, a period of tremendous advancement in endovascular techniques. During time interval of 1980s, 1990s, and 2000s, the mortality rate of embolized patients declined from 17% to 12%. The complication rate dropped from 45% to 35%. The proportion of the poor outcome decreased from 51% to 28%; moreover, the proportion of the good outcome increased from 49% to 70%. The results suggest that advances in endovascular treatment have greatly improved the outcome of patients with VGAMs. With the development of science and technology, endovascular techniques have become more advanced, and thus are more beneficial to patients. Embolization treatment achieved so much progress that other methods such as microsurgery, Gamma Knife surgery, and medical management cannot be compared with endovascular treatment, especially in terms of the mortality rate.³¹

Limitations

Although our meta-analysis results are provocative, several limitations should be taken into consideration. Our review included a small number of subjects, mainly due to the paucity of studies that have directly compared endovascular embolization with other approaches. Nevertheless, our findings are in accordance with the results of an extensive literature search, in which we identified studies conducted on diverse patient populations around the world. Therefore, we believe our results are also relevant to other populations.

As in many retrospective analyses, the limitations of the study include the lack of randomization. The systematic review can be affected by the selection, investigation, and reporting biases in this area of clinical research. First, Egger's test showed evidence of publication bias existing in the following areas: clinical outcome, mortality (total mortality, MEP, technical mortality, other reasons), and complications (cerebral hemorrhage, cerebral ischemia, hydrocephalus, and developmental delay). This bias may have been due to the fact that unreported data were not included or the absence of reporting of side effects of endovascular embolization for VGAMs. The number of published studies included in our meta-analysis was not sufficiently large for a comprehensive analysis. Second, there was significant heterogeneity among the studies in terms of the different groups evaluated, which could have influenced the accuracy of our evaluation of endovascular embolization.

However, on the side of publication bias, using systematic reviews to find relevant studies to answer a question could be considered an unusual technique, but we do not

think that this led us to "biased" results. All of the included systematic reviews used very comprehensive search strategies. By using Begg's test and Egger's test, we were able to quantify the publication bias effect sizes. Publication bias occurs when medical journals publish more studies favoring one intervention than studies favoring another one. Publication bias would be particularly frequent for studies with a small sample size. Second, on the other side, there is the quality of the evidence. Blinding was usually not used in these studies. For the endovascular embolization for VGAMs, blinding of participants is not feasible and blinding of study personnel is unrealistic, at least for the intraoperative and immediate postembolization periods. As stated above, publication bias exists in our studies, which resulted in degrading of the quality of the studies. However, our goal is to invite the trial authors to make a clear statement on the mortality and complications of the techniques that they were studying. Third, although we did not find evidence of specific contributors to heterogeneity in this review, we think that heterogeneity might be related to differences in the interventions and study design, details of which are routinely underreported in trials.

Thus, publication bias partially influenced the results of the meta-analysis. Subgroup analyses in this review were limited by the available data, which indicates that our results and their potential clinical application should be interpreted with caution. However, these limitations could be attributed to differences in patient outcome. Further analyses with individual patient data from large, multicenter, prospective, randomized controlled double-blind trials and observational studies would be more informative.

Conclusions

The successful treatment of VGAMs remains a complex therapeutic challenge. The results of our meta-analysis give a clear indication that endovascular treatment should be the first option for VGAMs. Our literature analysis suggests that vein of Galen malformations with endovascular embolization can result in acceptable the rate of mortality, complications, and good clinical outcome. Above all, the timing and course of endovascular treatment is dictated by the clinical presentation of the patient. This therapeutic window represents the optimal time for treatment. Intracerebral hemorrhage and venous thrombosis can be avoided, to a large extent, by staging the embolization procedure. The goal is not complete occlusion of the lesion, but rather partial obliteration to redistribute blood flow to allow for normal cardiac and neurological development. Future multicentered, randomized trials are necessary to confirm these findings as the number of studies included in this analysis was small in scale.

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