Treatment of Intracranial Dural Fistulas with Onyx: A Prospective Cohort, Systematic review, and Meta-Analysis

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Short Title: Treatment of Intracranial Dural Fistula with Onyx

ABBREVIATIONS: **DAVF** = dural arteriovenous fistula; **EVT** = endovascular treatment; **DSA** = digital substraction angiography; **CI** = confidence interval; **DMSO** = dimethyl-sulfoxide

Key Words: endovascular treatment; meta-analysis; embolization; dural fistula; onyx; treatment outcome.

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Background: Onyx is important embolic material in the treatment of intracranial dural arteriovenous fistula (DAVF). However, its impact on DAVF occlusion rates, morbidity, mortality, and complication rates is not fully examined.

Objective: To improve understanding of safety and effectiveness profiles associated with Onyx treatment of intracranial DAVF

Methods: We analyzed data from our prospective clinical registry and conducted a systematic review of all previous studies using Onyx published between January 2005 and December 2015 in MEDLINE and EMBASE.

Results: In the prospective study, 41 procedures were performed in 33 consecutive patients harboring 36 DAVFs. Complete initial exclusion was obtained in 32 of 36 (88.9%) fistulas; 31 fistulas were followed-up showing 4 (12.9%) recurrences. Procedure-related morbidity and mortality was 3% and 0%, respectively. The literature search identified 19 previous involving 425 patients with 463 DAVFs. Meta-analysis showed an initial complete occlusion rate of 82% (95% confidence interval [CI]: 74%, 88%; I^2, 70.6%), and recurrence rate at mid-term of 2% (95% CI: 0%, 5%; I^2, 21.5%). Pooled post-operative neurologic deficit, procedure-related morbidity, and mortality rates were 4% (95% CI: 2%, 6%; I^2, 0%), 3% (95% CI: 1%, 5%; I^2, 0%) and 0%, respectively.

Conclusion: This meta-analysis suggests that endovascular treatment with Onyx is a safe treatment modality for DAVFs. Although Onyx showed a low recurrence rate at mid-term, the long-term risk is poorly addressed in our study and should warrant a longer follow-up.

Intracranial dural arteriovenous fistulas (DAVFs) account for 10 to 15% of intracranial vascular malformations and are treated by endovascular approach in the majority of cases (1). Ethylene vinyl alcohol/dimethyl sulfoxide polymer (Onyx; EV3, Irvine, California) is an important liquid embolic material in the endovascular treatment (EVT) of intracranial DAVFs. Onyx embolic material has been extensively used due to its non-adhesive properties, allowing prolonged injection times with good lesion penetration, and convenient control for the operator (2). Since the introduction of Onyx in 2005, several single-center studies have demonstrated acceptable rates of DAVF occlusion, morbidity, and mortality for patients treated with Onyx via trans-arterial approach (3-21).

Improved understanding of safety and effectiveness profiles associated with Onyx treatment of intracranial DAVF is needed. Thus, we analyzed data from our prospective clinical registry and conducted a systematic review and meta-analysis of the literature with special interest on intracranial DAVF occlusion rates, procedure-related complication rates, and recurrence rates at follow-up for intracranial DAVFs treated with Onyx via trans-arterial approach.

MATERIALS AND METHODS

Prospective Study

Patients.-This study was approved by the local ethics committee and was found to conform to scientific principles and research ethics standards. An informed consent was obtained from each patient. This study was designed, conducted, and analyzed and the article was written independently of industry or any other financial support.

The population was nested within a longitudinal cohort of consecutive patients who were referred to our institution for EVT of intracranial DAVFs between January, 2013, and December, 2015. This prospectively maintained database was queried retrospectively to identify all consecutive patients matching the following inclusion criteria: *(a)* patients with intracranial DAVFs (b) who were treated by trans-arterial approach using Onyx.

EVT and initial angiographic results.-All procedures were performed under general anesthesia and full heparinization. Complete selective digital subtraction angiography (DSA) was performed before treatment. An Onyx-compatible microcatheter was coaxially positioned into one of major arterial feeder as close as possible to the fistula site. First, the dead space of the microcatheter was flushed with dimethyl-sulfoxide (DMSO), followed by a slow injection of Onyx under subtraction fluoroscopy. If an Onyx reflux occurred, the injection was paused for 30 to 60 seconds. During Onyx progression into the shunt, it was continually and slowly injected. The removal of the microcatheter was done when the Onyx cast stopped advancing or if we had a complete occlusion of the shunt. A post-operative DSA was performed after the procedure to confirm the complete occlusion of the DAVF. Initial angiographic results of EVT were classified by a neuroradiologist not involved in the initial EVT (B.G., with 7 years of experience in neuroimaging) by using the Cognard classification (22).

Systematic standard follow-up protocol.-After discharge, the systematic follow-up included at least a clinical examination and DSA at 3 months after EVT for ruptured DAVFs and at 6 months for unruptured DAVFs.

Clinical follow-up.-Further clinical follow-up data were collected during hospitalization for follow-up DSA or external consultation at 3 months. Post-operative neurologic complication was defined as any new neurologic symptoms, including cranial nerve palsy. Procedure-related morbidity was defined as a permanent neurologic deficit including cranial nerve palsy or change in modified Rankin Scale (mRS) score≥1 at 3 months after the procedure.

Image acquisition and analysis.-Angiographic images were acquired in antero-posterior and lateral projections before and immediately after treatment. Angiographic images obtained immediately after EVT were compared with those obtained at angiographic follow-up. At follow-up, we considered a DAVF recurrence when an early venous opacification was observed at DAVF completely occluded regardless of how big it is. In addition, we also considered it as a recurrence when the type of DAVF was modified.

Systematic Review

We prepared this study in accordance with the Meta-analysis Of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (23,24), including objectives and plans for collecting and analyzing the data. We performed a systematic review of the literature by two authors (U.S.G., N.M.) using the keywords “dural arteriovenous fistula” and “onyx” and “cerebral” or “brain” or “intracranial” in MEDLINE and EMBASE databases. Inclusion criteria were the following: all type of study design published in English language, ≥10 patients, from January 2005 to December 2015, where EVT was performed via a trans-arterial route and where Onyx was used as the embolic material. Exclusion criteria were the following: case report, studies with duplicate case series, studies with balloon-assisted technique.

Baseline characteristics of patients and DAVFs.-Clinical data included sex, number of eligible patients, mean age of patients, and clinical presentation. DAVFs characteristics, procedure-related complications, morbidity and mortality, anatomical outcomes, and follow-up modality. All the data were reviewed and collected individually by two authors (S.G.U. and M.N.), and compared. Disagreements were discussed until a consensus was reached.

Outomes.-Only patients treated with Onyx alone were considered for the calculation of the post-operative complications, morbi-mortality rates after treatment and DAVF recurrence rates. End points included post-operative neurologic deficit after EVT, including cranial nerve palsy, and anatomic results obtained at DSA or magnetic resonance angiography. Post-operative neurologic complication was differentiating as ischemic and hemorrhagic.

Individual study quality assessment.-The included studies being uncontrolled, individual study quality was assessed using a checklist published by the National Institutes of Health for before-after (pre-post) studies with no control group (25). This 12-item checklist enables an assessment of uncontrolled studies and provides an overall quality rating. Quality assessment was performed independently by 2 authors (S.G.U. and M.N.).

Statistical analysis

Systematic review.-The 95% confidence intervals (CIs) of the estimates were built with the Wilson method. The estimate and the 95% CI of the mean percentage over all the studies were obtained for each outcome using a logistic mixed model with a random effect on the intercept in order to take into account the heterogeneity between the studies. In all analyses, inconsistency of findings throughout studies was assessed by using the p value and the I^2 statistic. We searched for publication bias using Egger's test for small-study effects and presented funnel plots. The meta-analyses were carried out using the metaprop Stata command (26) on Stata/SE 14.1 (Statacorp LP, College Station TX, USA).

RESULTS

Prospective Study

Population.-A total of 41 procedures were performed in 33 patients (21 men and 12 women, mean age, 57.4 years) harboring 36 DAVFs (3 patients had 2 DAVFs). Table 1 provides baseline characteristics. Initial clinical symptoms were 10 intracranial hemorrhages, 12 tinnitus, and 2 seizures, while the rest of the patients presented with incidentally discovered DAVFs.

Initial angiographic results.-According to Cognard's classification, 7 cases were type I, 3 cases were type II a, 8 cases were type II b, 2 cases were type II a+b, 8 cases were type III and 8 cases were type IV. Initial complete exclusion of the DAVFs was obtained in 32 of 36 (88.9%) DAVFs. DAVFs obliterations were achieved in 2 procedures for 5 patients and in 1 procedure for the other cases.

Of the 4 partial EVT, the type of DAVF was initially II a (Patient 2), one II b (Patient 15), one III (Patient 4) and one IV (Patient 13). After EVT, the type II b was reverted to type II a, and the type III in type I. For the type IV, the occlusion after EVT was partial because of high risk of facial nerve palsy due to important microcatheter reflux. Thus, considering these 4 patients, 2 procedures were partial due to the risk of nerve palsy or reversion into benign type.

Angiographic results at follow up.-Angiography was obtained in 29 patients harboring 31 DAVFs (Table 1). A recurrence was observed in 4 DAVFs (12.9%). The 10 initially ruptured DAVF were totally occluded at follow-up. For initial partial obliteration, 2 patients showed similar DAVF type (Patients 4 and 15), 1 patient presented complete fistula exclusion at follow-up (Patient 13; a complementary surgery was performed after EVT failure), and 1 patient presented a type II b (Patient 2).

Clinical complications.-A total of 3 patients had post-operative neurologic complication following EVT. Two patients presented a cranial nerve palsy: 1 had a third cranial nerve palsy after treatment of DAVF type IV located at the anterior temporal lobe with subsequent transitory diplopia and ophthalmoplegia, which completely resolved 3 months later; and 1 patient had a facial nerve palsy that quickly improved during the first few days, but partially persisted at 3 months follow-up after treatment of right lateral sinus fistula type II a+b. After treatment of her second DAVF type II b located in the superior longitudinal sinus, the patient (Patient 15, Table 1) presented with a left hemiplegia due to venous infarction, persistent at follow-up (mRS 2).

Procedure-related morbidity and mortality.-In our prospective cohort, the procedure-related morbidity was 3% (1/33 patients). There was no procedure-related mortality. One patient died due to a compressive hemorrhage in the posterior fossa due to a type III ruptured DAVF. The hematoma was located in the vermis, causing an obstructive hydrocephalus with subsequent ventricular shunt placement. Emergency embolization was performed without complication during procedure, but 1 month later the patient died from complications of the intracranial hematoma.

Systematic Review

Of the 424 records that were identified in the initial search, 309 were screened after removal of duplicates, and 280 were excluded at title or abstract level. Twenty-nine were articles were reviewed at full-text out of which 19 studies were selected for final analysis (Fig 1). At baseline, 425 patients harboring 463 DAVFs were included. Baseline patient and DAVF characteristics of the 19 included studies are shown in supplemental Table 1. The results of the meta-analysis, including the present study, are shown in Figure 2 and 3, and Table 2.

Initial angiographic results.-The overall initial complete occlusion rate was 82% (95% CI, 74%, 88%). Analysis of the data suggested significant heterogeneity across studies (p<0.05), the range of initial complete occlusion rate being 47%-100%.

Angiographic results at follow-up.-The recurrence rate was 2% (95% CI, 0%, 5%). Recurrence rate was reported at mid-term (mean follow-up, 5 months; range, 3 to 7.5 months (supplemental Table 2, online). Long-term DAVFs recurrences rates were reported in 2 studies comprising a small sample size of 45 patients.

Clinical complications.-The pooled post-operative neurologic complications rate was 4% (95% CI: 2%, 6%; I^2, 0%). The pooled rate of post-operative cranial nerve palsy was 2% (95% CI: 1%, 4%; I^2, 0%). The rate of cerebral ischemic and hemorrhagic complications rates were 1% (95% CI: 0%, 2%, I^2, 0%) and 0% (95% CI: 0%, I^2, 0%), respectively (supplemental Figure 1).

Procedure-related morbidity and mortality.-The pooled procedure-related morbidity rate was 3% (95% CI, 1%, 5%; I^2, 0%) with no statistically significant heterogeneity across studies. There were no procedure related deaths across the 17 studies.

Quality assessment.-Eighteen studies were retrospective whereas 1 was prospective. All were non-comparative. Studies had large heterogeneity in terms of methods for the assessment of outcomes (presence or not of an adjudication committee; presence or not of a centralized core laboratory; time of follow-up). Using the prespecified tool, the quality rating of studies was considered as fair or poor. The main limitations of studies were as follows: no prespecification of selection criteria for the study population; no justification of sample size; no independent assessment of outcome measures across all study participants. Consequently, the risk of bias was significant across studies. Furthermore, we identified potential publication bias on the rate of total complications. See supplemental Figure 1 and 2 (online) for funnel plot.

DISCUSSION

In our systematic review, the rate of recurrence at mid-term follow-up was low after EVT using Onyx of intracranial DAVFs (2%, 95% CI: 0%, 5%). Although this finding demonstrates the effectiveness of Onyx in the EVT of cranial DAFVs, we observed a non-negligible rate of DAVFs angiographic recurrence (12.9%) at 3-6 months in our prospective study. Results at follow-up of intracranial DAVFs beyond 1 year after EVT are not well known. Longer follow-up period were reported in 2 studies including only a small number of patients (45 patients). Chandra et al. observed 0 recurrence of 28 patients at 28 months mean follow-up (9), whereas Ambekar et al reported 3 (14.3%) recurrences of 21 patients at 14 months mean follow-up (4). This underlines the importance of long-term follow-up for DAVFs, especially for initially ruptured ones with the risk of rebleeding. However, we used DSA, which is the “gold standard” modality for follow-up of Onyx-treated DAVFs, in our study and the series included in the systematic review.

To date, there are several embolic materials to treat DAVFs by endovascular approach including n-butyl-cyanoacrylate (n-BCA), Onyx, polyvinyl alcohol particles, and coils. To date, the best embolic material for cranial DAVFs is not well known and comparative studies with good methodological standard are warranted, which is not the objective in the present study. However, Rabinov et al. compared the effectiveness of cranial DAVFs EVT with Onyx versus n-BCA (20) in single center study. Although the sample size was limited (56 fistulas), the initial complete occlusion rate reported for Onyx was 82% versus 33.3% for n-BCA. A superior durability of the occlusion with Onyx on follow-up was observed. In a recent single center series of 24 fistulas, the authors compared intracranial DAVFs embolization with Onyx versus n-BCA and coils, and they reported initial complete occlusion rate of 66% for Onyx versus 22% for n-BCA (27). A possible explanation is that DAVFs are complex and heterogenic lesions, with considerable anatomo-pathological diversity, influencing the difficulty of the access and EVT phase. Furthermore, heterogeneity in operator experience may be another explanation.

Procedure-related morbidity and mortality rates were uniformly low across the studies with pooled rates of 3% (95% CI, 1%, 5%) and 0%, respectively. This meta-analysis, including our registry data, demonstrates the safety of EVT of intracranial DAVFs with Onyx, most morbidity events related to cranial nerve palsy (2%; 95% CI: 1%, 4%). EVT via trans-arterial approach of lesions close to the skull base, as cranial DAVFs, carries an elevated risk for ischemic nerve injury (1). As Onyx embolization technique usually utilizes some degree of Onyx reflux, adequate safety margins should be considered appropriately to minimize inadvertent Onyx migration to clinically important vascular branches.

Our study had several limitations. First, the articles included in the systematic review contained a majority of retrospective studies with a limited number of patients; some included combined liquid embolic materials. Second, a small number of studies (2 of 20 studies, 45 of 465 patients, 19.6%) with long-term follow-up were eligible. Third, data presentation was not uniform among the source articles, especially for the procedure-related morbidity definition. Four, it is possible that some relevant studies were not taken into account in our systematic review. However, it is unlikely that this potential publication bias distorted strongly our findings because we found no evidence of such bias by examining the funnel plots.

CONCLUSION

EVT of intracranial DAVFs with Onyx via trans-arterial approach is a safe treatment modality for DAVFs. Although Onyx showed a low recurrence rate at mean follow-up of 5 months, the risk of long-term recurrence is poorly evaluated in our study, and should warrant a longer follow-up period, especially in ruptured cases and neuro-aggressive ones.

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Figure Legends:

Figure 1. Flowchart shows screening and selection of studies for meta-analysis.

Figure 2. Crude odds ratio for (A) initial complete occlusion, (B) recurrence at mid-term for each study and taking account of all the studies included in the meta-analysis

Figure 3. Crude odds ratios for (A) post-operative neurologic complications, and (B) cranial nerve palsy, and (C) procedure-related morbidity for each study and taking account of all the studies included in the meta-analysis.

Table Legends:

Table 1. Neurologic Hospital Baseline characteristics of patients and DAVFs.

Table 2. Meta-Analysis of Safety and Effectiveness of EVT with Onyx.

Figure1

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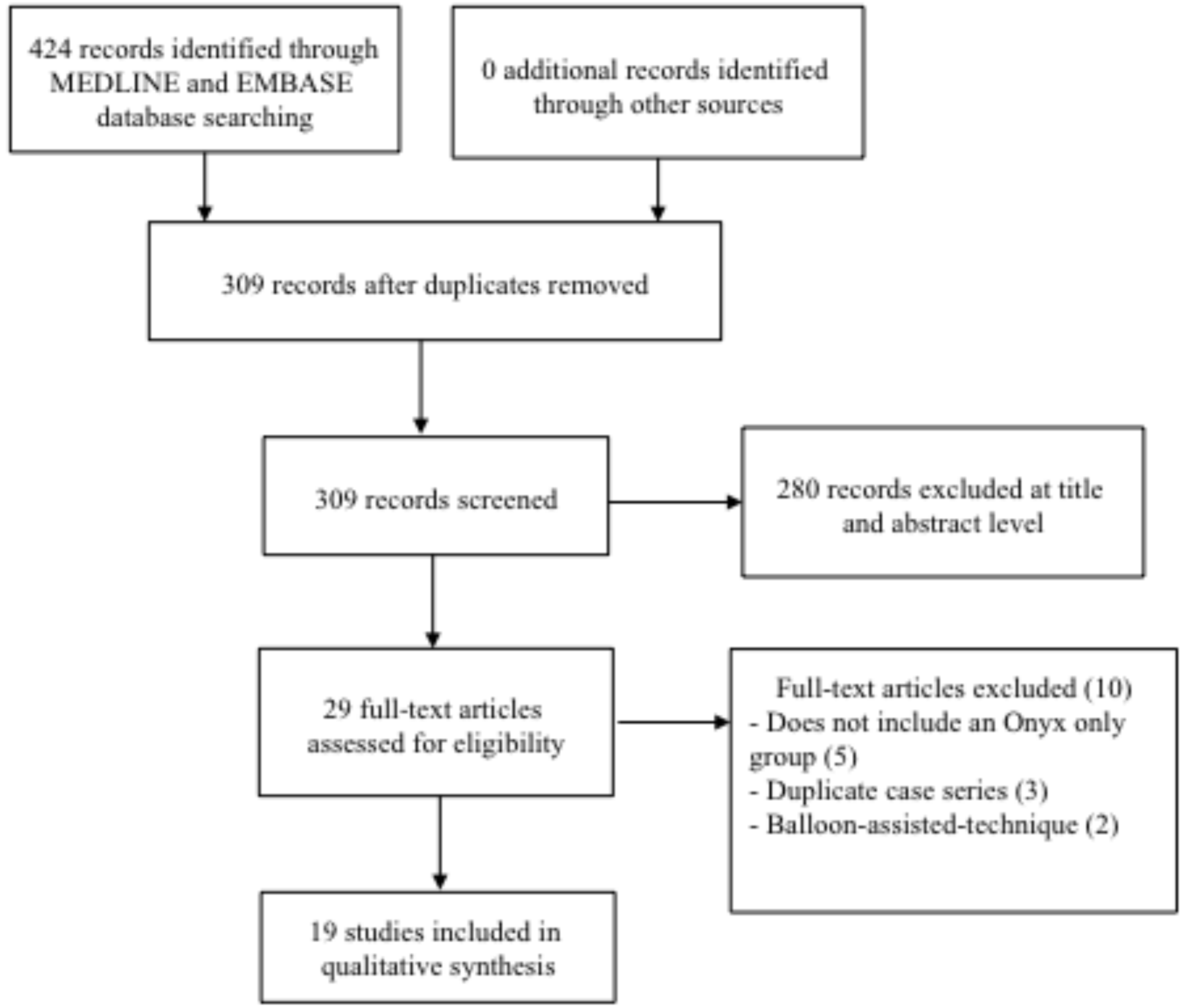

Figure2

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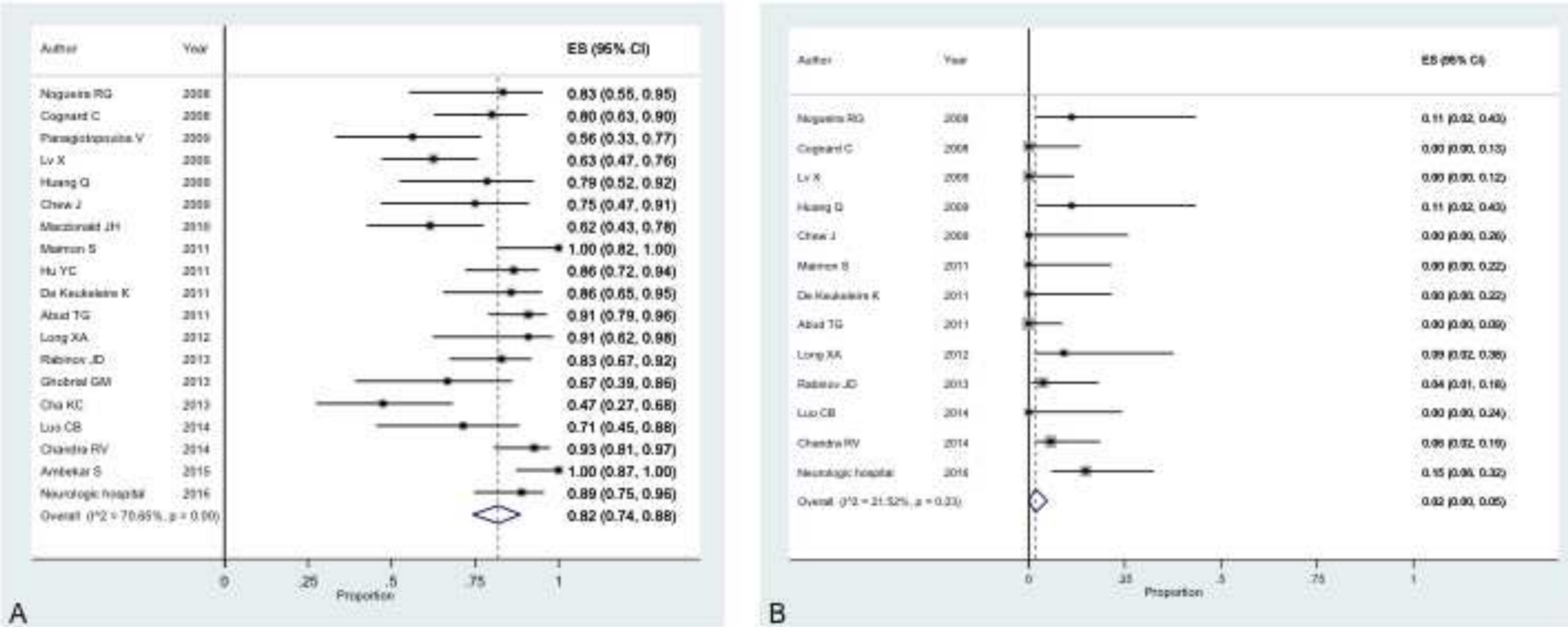

Figure3

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Table1

Table 1. Neurologic Hospital Baseline Patient and DAVF characteristics.

Patients	Sex	Age	Cognard Classification[23]	Symptoms	Access artery	Initial complete occlusion[‡]	Complication	Procedure-related morbidity	Recurrence[‡]
1	M	65	III	Non specific	MMA	Yes	No	0	NA
1[*]	M	65	IV	Hemorrhage	MMA	Yes	No	0	NA
2	F	39	II a	Tinnitus	MMA	Partial (I)	No	0	Recurrence (II b)
3	F	43	IV	Non specific	MMA	Yes	CNP (III)	0	NA
4	M	75	III	Hemorrhage	MMA	Partial (I)	No	0	Partial (type I)
5	F	64	I	Tinnitus	MMA	Yes	No	0	NA
6	M	62	I	Tinnitus	MMA	Yes	No	0	NA
7	M	70	IV	Hemorrhage	APA	Yes	No	0	No
8	M	71	II b	Non specific	MMA	Yes	No	0	No
9	F	38	III	Hemorrhage	MMA	Yes	No	0	No
10	F	59	II b	Tinnitus	MMA	Yes	No	0	No
11	M	50	II b	Non specific	MMA	Yes	No	0	No
12	M	46	II a	Tinnitus	MMA	Yes	No	0	No
13	F	78	IV	Hemorrhage	MMA	Partial	No	0	No[§]
14	M	66	I	Tinnitus	MMA	Yes	No	0	No
15	F	56	II b	Tinnitus	MMA	Partial (II a)	Ischemia	Yes	Partial (II a)
15[*]	F	56	II a+b	Tinnitus	MMA	Yes	CNP (VII)	0	Recurrence
16	F	45	III	Hemorrhage	PMA	Yes	No	0	No
17	M	57	II b	Non specific	MMA	Yes	No	0	Recurrence
17[*]	M	57	II a+b	Non specific	MMA	Yes	No	0	No
18	M	55	I	Tinnitus	MMA	Yes	Microcatheter fracture	0	No
19	M	54	IV	Seizure	MMA	Yes	No	0	No
20	F	47	II b	Tinnitus	MMA	Yes	No	0	No
21	F	42	I	Tinnitus	MMA	Yes	No	0	No
22	F	61	III	Hemorrhage	MMA	Yes	No	0	No
23	M	64	I	Tinnitus	MMA	Yes	No	0	Recurrence
24	M	68	IV	Non specific	OA	Yes	No	0	No
25	M	44	II b	Non specific	SCA	Yes	No	0	No

26	M	65	IV	Non specific	OA	Yes	No	0	No
27	M	50	III	Seizure	MMA	Yes	No	0	No
28	M	81	II b	Hemorrhage	MMA	Yes	No	0	No
29	M	73	II a	Non specific	OccA	Yes	No	0	No
30	F	48	I	Tinnitus	MMA	Yes	No	0	No
31	M	51	III	Hemorrhage	MMA	Yes	No	0	No
32	M	55	III	Non specific	MMA	Yes	No	0	No
33	M	52	IV	Hemorrhage	MMA	Yes	No	0	No

Note.-M, male; F, female; NA, non assessed; MMA, middle meningeal artery; OA, ophtalmic artery; OccA, occipital artery; PMA, posterior meningeal artery; SCA, superior cerebellar artery; APA, ascending pharengeal artery; CNP, cranial nerve palsy.

[*] Patients 1, 15 and 17 had 2 DAVFs.

[‡] Data in parentheses is the type of DAVF according Cognard classification (23).

[§] A complementary surgery was performed after initial EVT failure.

Table2

Table 2. Meta-analysis of safety and efficacy after EVT with Onyx

Outcomes	Number of studies	Sample size	Pooled rates (95% CI)	Heterogeneity	
				p value	I^2
Cranial nerve palsy (*n = 13*)	16	466*	2% (1%, 4%)	0.96	0.0%
Post-operative neurologic complications (*n = 22*)	16	466*	4% (2%, 6%)	0.94	0.0%
Procedure-related morbidity (*n = 17*)	16	366**	3% (1%, 5%)	0.53	0.0%
Procedure-related mortality (*n = 0*)	17	366**	0% (0%, 0%)	1	0.0%
Initial complete obliteration (*n = 373*)	19	463***	82% (74%, 88%)	<0.05	70.6%
Recurrence (*n = 5*)	13	263***	2% (0%, 5%)	0.23	21.5%

* Number of procedures

** Number of patients

*** Number of DAVFs

Supplemental Tables:

Supplemental Table 1. Population Baseline Characteristics of the 19 Studies.

Author	Year	Sample size	Number of DAVFs	Mean age	Number of procedures	Number of symptomatic	Number of seizure	Number of hemorrhage	Number of tinnitus
Nogueira RG	2008	12	12	56	17	9	0	4	2
Cognard C	2008	30	30	62,4	35	28	4	16	2
Panagiotopoulos V	2009	16	16	61	24	15	NA	5	NA
Lv X	2009	40	40	43,1	40	40	0	16	10
Huang Q	2009	14	14	50	15	14	0	12	0
Chew J	2009	12	12	53,4	13	10	1	3	1
Saraf R	2010	36	NA	NA	NA	NA	NA	NA	NA
Macdonald JH	2010	NA	26	NA	28	NA	NA	NA	NA
Maimon S	2011	17	17	56	20	16	1	5	3
Hu YC	2011	33	37	NA	39	33	NA	NA	NA
De Keukeleire K	2011	20	21	57,2	25	20	1	7	8
Abud TG	2011	42	44	56	46	40	2	6	16
Long XA	2012	11	11	51,6	11	11	3	0	10
Rabinov JD	2013	34	35	56,1	54	34	2	13	14
Ghobrial GM	2013	12	12	NA	40	12	NA	NA	NA
Cha KC	2013	19	19	61	22	15	0	4	2

Luo CB	2014	14	14	62	14	14	1	2	4
Chandra RV	2014	40	41	57	49	30	2	13	14
Ambekar S	2015	26	26	55,4	28	17	0	8	4

Data are number of patients or DAVFs for which information was available.

Supplemental Table 2. Outcomes of the 19 Studies.

Author	Technical complications	Cranial nerve palsy	Post-operative neurologic complications	Procedure-related morbidity	Morbidity definition	Procedure-related mortality	Initial complete occlusion	Recurrence	Time of follow-up*
Nogueira RG	0	0	0	0	NA	0	10	1	4.4
Cognard C	1	1	2	2	NA	0	24	0	3
Panagiotopoulos V	0	0	1	0	Permanent deficit	0	9	1	3.7
Lv X	2	2	4	3	mRS	0	25	0	5.4
Huang Q	1	0	1	0	NA	0	11	1	7.5
Chew J	1	0	0	0	NA	0	9	0	3.6
Saraf R	NA	NA	NA	NA	NA	0	33	0	6
Macdonald JH	NA	NA	NA	0	NA	0	16	0	NA
Maimon S	1	1	1	0	Permanent neurologic deficit	0	17	0	7.5
Hu YC	NA	NA	NA	NA	Permanent complication	0	32	NA	NA
De Keukeleire K	5	1	2	2	Permanent neurologic deficit	0	18	0	6.5
Abud TG	0	2	2	1	NA	0	40	0	6
Long XA	2	0	0	0	NA	0	10	1	4.5
Rabinov JD	4	2	2	3	Major neurological adverse events	0	29	1	3
Ghobrial GM	0	0	2	3	NA	0	8	NA	NA

Cha KC	0	0	0	0	NA	0	9	NA	NA
Luo CB	2	0	0	0	NA	0	10	0	NA
Chandra RV	5	2	2	1	Permanent neurologic complication	0	38	2	4.2
Ambekar S	NA	NA	NA	NA	NA	0	26	NA	NA

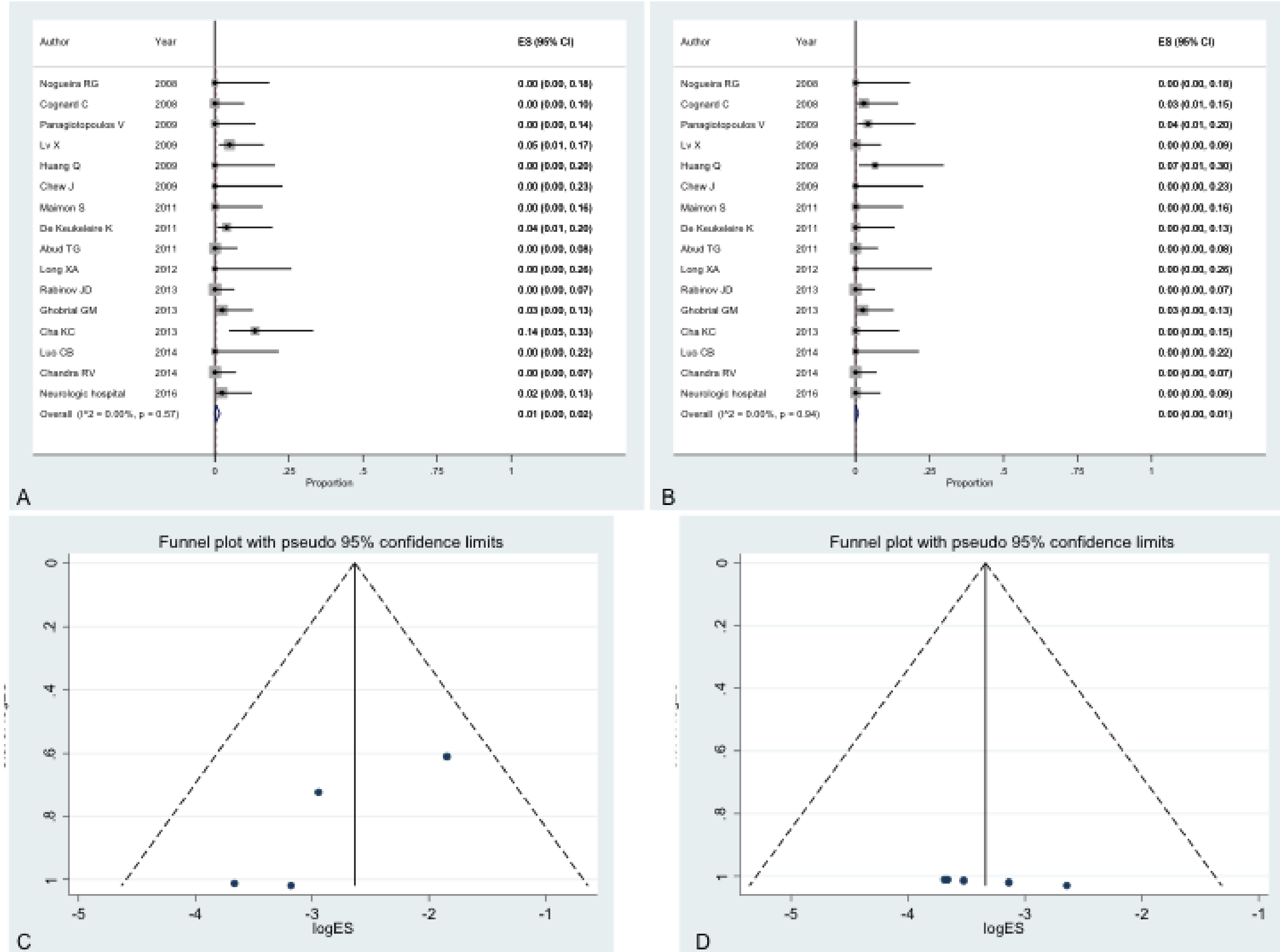
Note.-NA, not assessed.

Data are number of patients or DAVFs for which information was available.

* Data are months

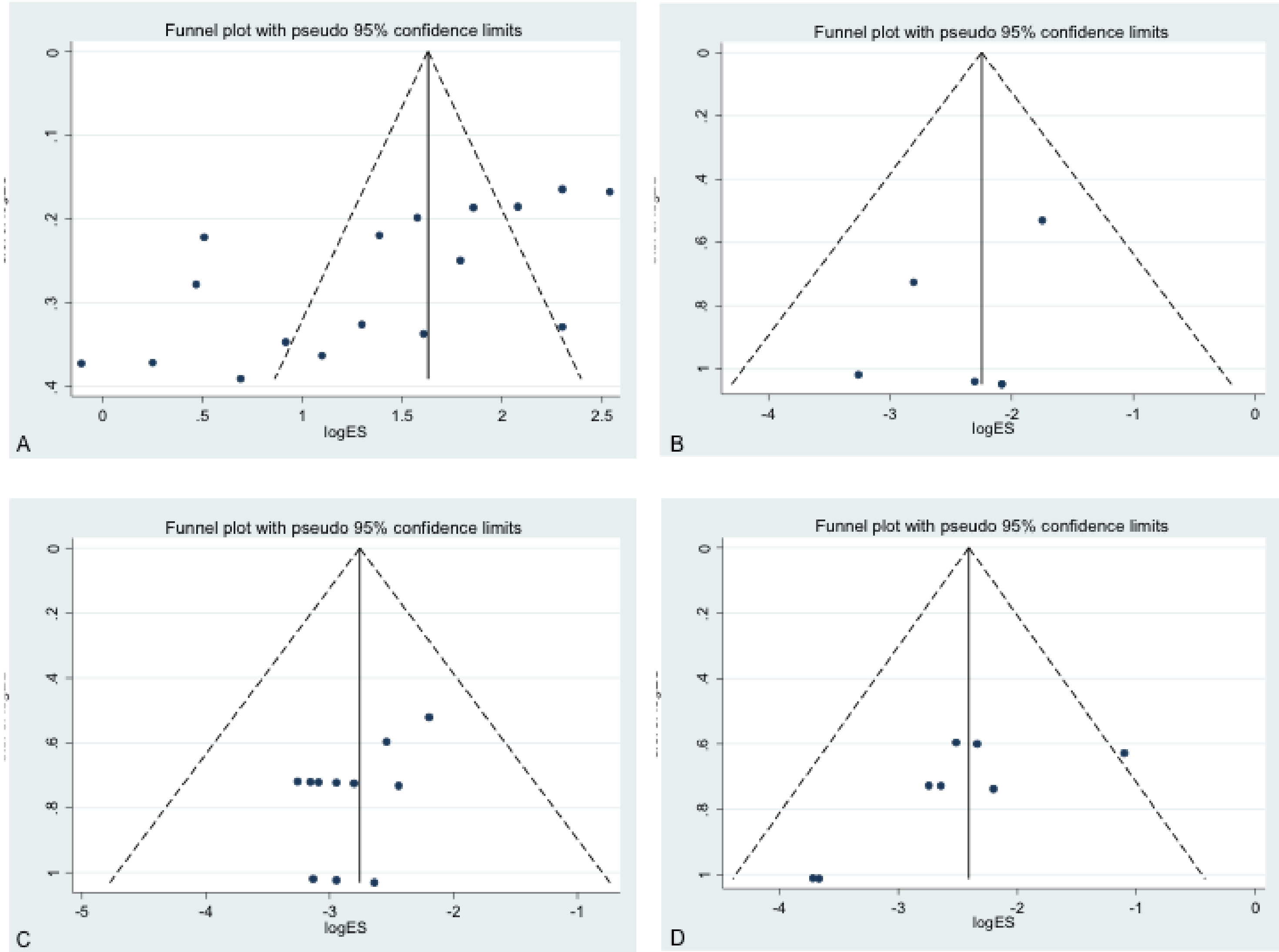
Supplemental Figures :

Supplemental Figure 1. Crude odds ratios for (A) ischemic cerebral complications, (B) hemorrhagic cerebral complications, (C) funnel plot for ischemic complications, and (D) funnel plot for hemorrhagic complications.



Author
Year
ES (95% CI)
Nogueira RG
2008
0.00 (0.00, 0.18)
Cognard C
2008
0.00 (0.00, 0.10)
Panagiotopoulos V
2009
0.00 (0.00, 0.14)
Lv X
2009
0.05 (0.01, 0.17)
Huang Q
2009
0.00 (0.00, 0.20)
Chew J
2009
0.00 (0.00, 0.23)
Maimon S
2011
0.00 (0.00, 0.16)
De Keukeleire K
2011
0.04 (0.01, 0.20)
Abud TG
2011
0.00 (0.00, 0.08)
Long XA
2012
0.00 (0.00, 0.26)
Rabinov JD
2013
0.00 (0.00, 0.07)
Ghobrial GM
2013
0.03 (0.00, 0.13)
Cha KC
2013
0.14 (0.05, 0.33)
Luo CB
2014
0.00 (0.00, 0.22)
Chandra RV
2014
0.00 (0.00, 0.07)
Neurologic hospital
2016
0.02 (0.00, 0.13)
Overall (I^2 = 0.00%, p = 0.57)
0.01 (0.00, 0.02)
0
.25
.5
.75
1
Proportion
A
Author
Year
ES (95% CI)
Nogueira RG
2008
0.00 (0.00, 0.18)
Cognard C
2008
0.03 (0.01, 0.15)
Panagiotopoulos V
2009
0.04 (0.01, 0.20)
Lv X
2009
0.00 (0.00, 0.09)
Huang Q
2009
0.07 (0.01, 0.30)
Chew J
2009
0.00 (0.00, 0.23)
Maimon S
2011
0.00 (0.00, 0.16)
De Keukeleire K
2011
0.00 (0.00, 0.13)
Abud TG
2011
0.00 (0.00, 0.08)
Long XA
2012
0.00 (0.00, 0.26)
Rabinov JD
2013
0.00 (0.00, 0.07)
Ghobrial GM
2013
0.03 (0.00, 0.13)
Cha KC
2013
0.00 (0.00, 0.15)
Luo CB
2014
0.00 (0.00, 0.22)
Chandra RV
2014
0.00 (0.00, 0.07)
Neurologic hospital
2016
0.00 (0.00, 0.09)
Overall (I^2 = 0.00%, p = 0.94)
0.00 (0.00, 0.01)
0
.25
.5
.75
1
Proportion
B
Funnel plot with pseudo 95% confidence limits
0
.2
.4
.6
.8
1
-5
-4
-3
-2
-1
logES
C
Funnel plot with pseudo 95% confidence limits
0
.2
.4
.6
.8
1
-5
-4
-3
-2
-1
logES
D

Supplemental Figure 2. Funnel plots for (A) initial complete obliteration; (B) recurrence at mid-term; (C) post-operative neurologic complications; and (D) procedure-related morbidity.


Funnel plot with pseudo 95% confidence limits
logES
A
Funnel plot with pseudo 95% confidence limits
logES
B
Funnel plot with pseudo 95% confidence limits
logES
C
Funnel plot with pseudo 95% confidence limits
logES
D