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Transvenous Embolization of Brain Arteriovenous Malformations: Up-to-Date Meta-Analysis

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ABSTRACT

AIM: To conduct an up-to-date meta-analysis to assess the success and complication rates of transvenous embolization (TVE) of brain arteriovenous malformations (BAVMs), and to determine its efficacy and safety.

MATERIAL and METHODS: Relevant and potentially relevant studies from 1982 to February 2021 were searched; after which those that satisfied our eligibility criteria and reported the main outcomes (endovascular occlusion and complication rates) were included.

RESULTS: Ultimately seven studies were selected. In total, 154 patients were comprehensively reviewed for BAVMs characteristics and endovascular TVE techniques. The weighted mean rate of immediate endovascular total occlusion, overall technical complication, and overall good functional outcome (mRs < 2) were 93% (95% confidence intervals (CI), 89.1%–96.9%, I2 = 0%, p=0.487), 10.5% (95% CI, 4.3%–16.6%, I2 = 30.8%, p=0.193), and 90.9% (95% CI, 85.3%–96.6%, I2 = 26.6%, p=0.241), respectively.

CONCLUSION: TVE for BAVMs was found to be generally safe and effective in certain selected patients. However, the complementary role of TAE to TVE as a definitive endovascular treatment for BAVMs cannot be separated. More studies regarding this role need to be conducted.

KEYWORDS: Transvenous, Embolization, Endovascular, Brain, Arteriovenous malformations

ABBREVIATIONS: AVMs: Arteriovenous malformations, **BAVMs:** Brain arteriovenous malformations, **DAVF:** Dural arteriovenous fistulas, **ICH:** Internal cerebral hemorrhage, **PROSPERO:** International prospective registry of systematic reviews, **IVH:** Intraventricular hemorrhage, **mRs:** Modified Rankin score, **NICE:** National institute for health and clinical excellence, **SAH:** Subarachnoid hemorrhage, **TAE:** Transarterial embolization, **TVE:** Transvenous embolization, **TRENSH:** Transvenous retrograde nidus sclerotherapy under controlled hypotension

INTRODUCTION

Brain arteriovenous malformations (BAVMs) usually present as brain hemorrhage with an annual risk of bleeding of 2%–4%. Arteriovenous malformations (AVMs) remain challenging to treat given their variable pathological patterns, location, and unpredictable hemodynamics (1,2).

Transarterial embolization (TAE) has been primarily used to reduce the size of large AVMs, enhance surgical safety, or make AVMs amenable to radiosurgery (2,24,10). Independent curative TAE rarely exceeds 50% (8,18). Despite the recent advancements in endovascular modalities, TAE remains challenging to perform in some AVMs given their plexiform nature, distant location of the nidus, and presence of small tortuous arterial feeders to access (8).

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As such, transvenous embolization (TVE) of BAVMs has evolved as a potential novel therapy in the past few years with promising variable results (6,18,22,27). The current meta-analysis aimed to assess the success and complication rates of the TVE and determine its efficacy and safety.

MATERIAL and METHODS

Review Registration

The review was registered in the International Prospective Registry of Systematic Reviews with registration number: CRD42021236884.

Literature Search

The literature review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (20). Electronic databases were searched using the following keywords: “Arteriovenous malformation,” “Brain,” “endovascular,” “transvenous,” and “Embolization.” Four biomedical databases, namely PubMed, Web of Science, Scopus, and Science Direct were searched for relevant and potentially relevant studies from 1982 to February 2021 as shown in Figure 1. Title screening was done, followed by exclusion of noneligible studies and duplicate results. Thereafter, abstract screening was conducted; after which conference abstracts, reviews, and case reports were excluded. Finally, the remaining publications underwent full-text screening.

Inclusion and Exclusion Criteria

All studies published in English, including comparative studies, case series, and randomized control trials, which reported on the outcomes of TVE for BAVMs were considered and included. We excluded abstracts, case reports, reviews, letters to the editor, editorials, and meta-analyses. Studies reporting less than four patients and those that did not report the main outcomes (endovascular occlusion and complication rates) were also excluded. Authors who had published more than one study with potential overlapping data were contacted, which was followed by a comprehensive assessment of their studies. Only studies with consecutive patients were included.

Risk of Bias Assessment

All studies were evaluated according to the National Institute for Health and Clinical Excellence checklist (26).

Data Extraction and Outcomes

1. Authors’ name, country, year of publication, and the time interval in which the study was carried on.
2. Patient characteristics (their age and sex), ruptured BAVMs (accompanied with cerebral hemorrhage), BAM grade according to the Spetzler–Martin grading scale, pathological type (size of BAVM nidus, location, and pattern of venous drainage), number of arterial feeders and draining veins, and number of patients with previous treatment.
3. Technical aspects of TVE and any combined procedures.
4. Postprocedural complications, including postprocedural cerebral hemorrhage.

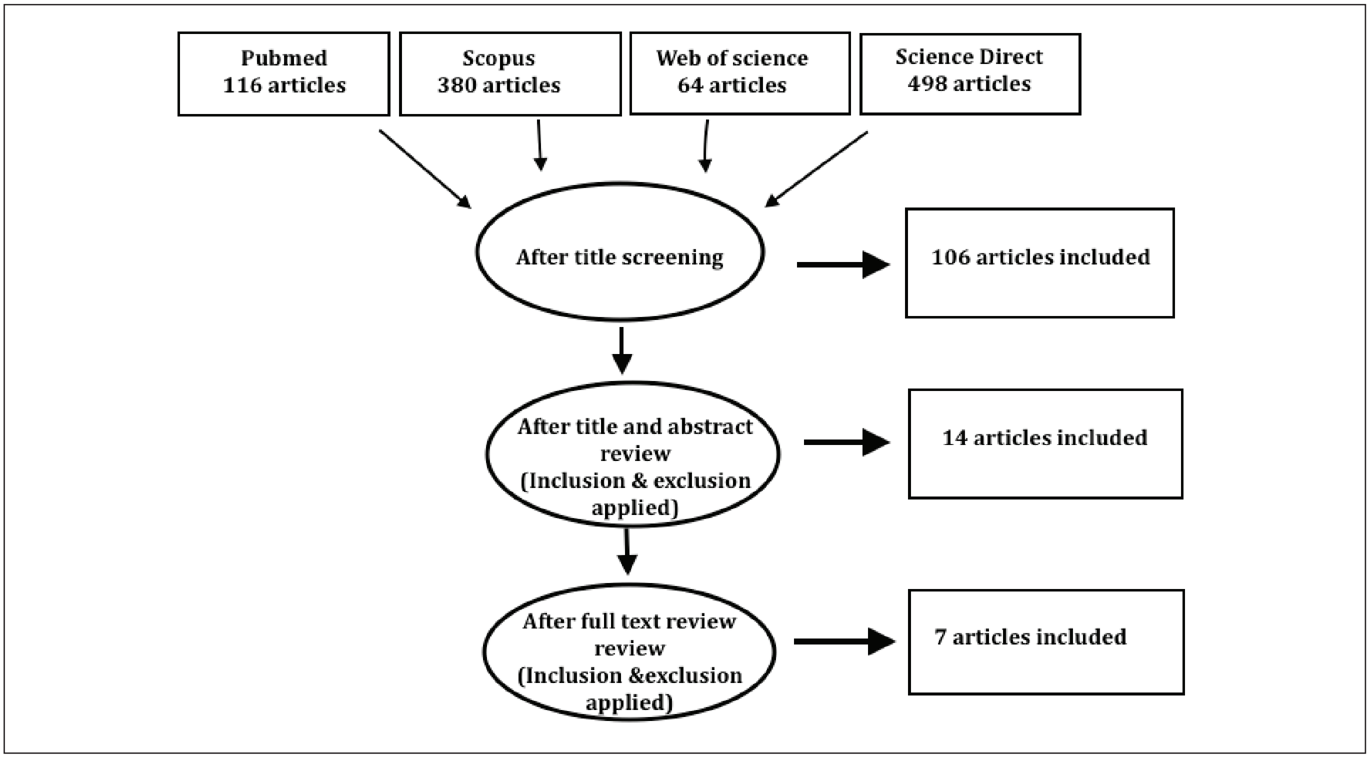

Figure 1: Prisma diagram.

5. Follow-up duration and good functional outcome, defined as a modified Rankin score (mRs) of 0 to 2 at follow-up.
6. Endovascular occlusion of BAVMs.
7. Technical failure of the procedure, recurrence, and reports of subsequent complementary management.

Assessment of Publication Bias Among the Studies Included

According to Lau et al., the assessment of publication bias using funnel plot or other tests requires at least 10 studies (19). Thus, publication bias assessment was not possible given the small number of studies included (n=7) in this review.

Statistical Analysis

The main investigator entered the extracted data into an Excel sheet (Microsoft). Variables, such as mean, range, numbers, and percentages of patients, were reported. Meta-analysis was conducted using openMeta (Analyst) ™ version 12.11.14, an open-source software for advanced meta-analysis. Data were pooled and reported as weighted mean rates and their 95% CI. Heterogeneity among studies was evaluated by calculating the p values of the Q test in addition to measuring the inconsistency (I_2) index

RESULTS

Studies and Patient Characteristics

Seven studies published from 2013 to 2020 (5,6,13-18) that satisfied the eligibility criteria were ultimately selected (Online Supplementary Diagram 1). Among these studies, five were retrospective, whereas two were prospective. The quality of the studies is summarized in Table I.

In total, 154 patients were reviewed, 55.8% of whom were males. The patients' age ranged from 7–78 years, with a mean age of 34 years. The follow-up duration ranged from 1–26 months (Table II).

The nidus size before treatment was <3 cm in 106 patients. A superficially (cortical) located nidus was found in 82 patients whereas a single draining vein was observed in 128 patients. Deep venous drainage was found in 83 patients. Intracranial hemorrhage (AVM rupture) was present in 119 patients. Regarding the Spetzler-Martins grading scale, 73, 34, 23, and 22, were G III, G II, G I, and G IV, respectively, with only 2 patients being G V. Prior treatment was reported in 47 cases, which included surgical treatment (1 case), radiosurgery (2 cases), and TAE (44 cases). The BAVMs characteristics are shown in Table III.

Technical Aspects of TVE

Five studies (4,7,12,17,33), performed TVE through the transjugular venous route, one study (14) utilized the transfemoral route, and one study (15) did not specify the route utilized. In all studies, both detachable and nondetachable microcatheters were used, including Marathon, Echelon, Sonic, and Apollo, Balt, and Headway. The EVOH copolymer (Onyx-18, Medtronic; and Squid-12, Emboflu, Gland, Switzerland) and precipitating hydrophobic injectable liquid (MicroVention, Tustin, California) were applied in most of the cases in all studies.

Table I: Illustrating the Assessment of Methodological Qualities of Case Series Studies Included in the Review

Items	Multicenter study	Clearly defined objective	Reported inclusion and exclusion criteria	Clearly defined outcomes	Prospective data collection	Patients were recruited consecutively	Clearly described results of the study	Stratified outcomes	Total score*
De Sousa et al., 2020 (7)	0	1	1	1	1	1	1	1	7
He et al., 2019 (12)	0	1	1	1	1	1	1	1	7
Koyanagi et al., 2020 (18)	0	1	1	1	0	1	1	1	6
Viana et al., 2017 (33)	0	1	1	1	0	1	1	1	6
Consoli et al., 2013 (5)	0	1	1	1	0	0	1	1	5
Renieri et al., 2015 (28)	0	1	1	1	0	0	1	1	5
Kessler et al., 2011 (17)	0	1	0	1	0	1	1	1	5

(*) *The quality of the studies was considered good (score = 7–8), fair (score = 4–6), or poor (score = 0–3).*

Table II: The Characteristics Included Studies

Study	Country	Time interval	Design	Patients number	Mean age	Sex	Follow up duration	Methodological quality
De Sousa et al., 2020 (7)	France	January 2008 and July 2019	Pro-spective	57	38.05	M (29) F (28)	6 months	Good
He et al., 2019 (12)	China	November 2016 and November 2018	Pro-spective	21	29.9	M (14) F (7)	2-26 months	Good
Koyanagi et al., 2020 (18)	Germany	December 2004 and February 2017	Retro-spective	51	47	M (31) F (20)	1-12 months	Fair
Viana et al., 2017 (33)	Brazil	January 2011 and November 2016	Retro-spective	12	33.4	M (5) F (7)	6 months	Fair
Consoli et al., 2013 (5)	Italy	February and April 2012.	Retro-spective	5	33.2	M (2) F (3)	6 months	Fair
Renieri et al., 2015 (28)	Italy	April 2011 and September 2012	Retro-spective	4**	11	M (2) F (1)	6 months	Fair
Kessler et al., 2011 (17)	France	June 2007 and March 2009	Retro-spective	5	41.9	M (3) F (2)	6 months	Fair
Total number of patients				154				

***(**)** One case was excluded as it was repeated in Consoli et al and considered an overlap.*

Combined TAE and TVE were performed in 48 patients. Venous balloon assist navigation and the pressure cooker technique (Coil embolization for the draining vein) were utilized in 13 and 87 patients, respectively. Arterial inflow control during TVE was performed in 35 patients. Technical failure was documented in four patients (Table IV).

Outcome

The immediate (primary) endovascular total occlusion weighted mean rate was 93% (95% CI, 89.1%–96.9%, I^2=0%, p=0.487). The weighted mean rate of residual detected on angiography was 6.7% (95% CI, 2.8%–10.6%, I^2=0%, p=0.799). None of the 140 patients who underwent follow-up digital subtraction angiography after 3 months or more showed recurrence; however, 2 patients showed progressive occlusion later on. Moreover, two patients required further treatment, among whom one underwent radiosurgery and the other underwent another TVE session. The overall technical complication weighted mean rate was 10.5% (95% CI, 4.3%–16.6%, I^2=30.8%, p=0.193). One nonprocedure-related death was reported in only one study. The overall weighted mean rate of good functional outcome was 90.9% (95% CI, 85.3%–96.6%, I^2=26.6%, p=0.241) (Figure 2).

Technical Complication and Hemorrhage

One patient developed cerebral infarction, whereas 18 patients developed internal cerebral hemorrhage (ICH). The following ICH types were observed: subarachnoid hemorrhage in four patients, three of which resulted from cerebral vessel perforation during microcatheter navigation; cerebral hematoma and intraventricular extension in five patients; sole intraventricular hemorrhage (IVH) in six patients; and sole cerebral hematoma in three patients. Among the aforementioned patients, 9 (50%) had good functional outcomes (i.e., mRs < 2) (Table V).

DISCUSSION

Evolution of TVE

TVE is a retrograde technique that can be accomplished with the induction of systemic and local hypotension to control intranidal pressure (4). This technique had first been utilized for transverse sigmoid dural arteriovenous fistulas (DAVF), vein of Galen malformation, and carotid-cavernous fistula (4,11). Massoud and Hademenos in 1999 had been the first to create a model for transvenous embolization of AVMs, which was described as the transvenous retrograde nidus sclerotherapy under controlled hypotension (TRENSH) technique (4,23). Since then, TVE for BAVMs has been increasingly utilized.

Therapeutic Options for BAVMs

Microsurgery could achieve definitive treatment for several cases with BAVMs. However, significant morbidity rates and permanent postoperative deficits have been reported (16,30). Nonetheless, not all BAVMs can be obliterated by radiosurgery, with complete obliteration requiring extended periods of time to occur. Radiation can cause tissue injury in the adjacent brain tissues with subsequent morbidities (25,31). TAE has been used as a palliative treatment or in combination with both microsurgery and radiosurgery. With the recent advancements in endovascular devices, liquid embolizing agents, and techniques, experts have attempted to achieve curative embolization and improve neurological outcomes (15,32). However, total occlusion of BAVMs with detachable or nondetachable microcatheters remains difficult

Table III: Summary of AVMs Characteristics and Pervious Treatment

Studies	Cases number	AVM rupture	AVM location	AVM Spetzler MARTIN	AVM drainage Pattern	AVM nidus size (M, range)	Arterial feeders	Number of draining veins / patients	Prior treatment
De Sousa et al., 2020 (7)	57	38	Deep (16) Superficial (41)	I 5 patients II 18 patients III 23 patients IV 10 patients V 1 patients	Superficial 25 Deep 28 Superficial and deep 4	M (2.44cm) (<3cm) 44 AVM	Not mentioned	(1) 37 patients (2) 18 patients (3) 2 patients	None
He et al., 2019 (12)	21	21	Deep (18) Superficial (3)	I 3 patients II 4 patients III 11 patients IV 3 patients	Superficial 11 Deep 9 Deep and superficial 1	M (2.76cm) (>3 cm) 9 AVM	Not mentioned	(1) 20 patients (>1) 1 patient	None
Koyanagi et al., 2020 (18)	51	42	Deep (30) Cortical (21)	I 9 patients II 6 patients III 26 patients IV 6 patients V 1 patient	Superficial 21 Deep 30	M (NAD) (< 3cm) 34 AVM (3cm-<6cm) 12 AVM (>6cm) 5 AVM	Not mentioned	(1) 49 patients (2) 2 patients	33
Viana et al., 2017 (33)	12	9	Superficial (12)	I 4 patients II 5 patients III 2 patients IV 1 patient	Superficial 9 Deep 2 Deep & superficial 1	M (1.9 cm) (<3CM) 8 AVM	9 AVM anterior circulation 3 AVM posterior circulation 2 AVM perforators	(1) 10 patients	9
Consoli et al., 2013 (5)	5	5	Deep (5)	III 5 patients	Deep and superficial 1 Deep 4	M (NAD) (<3 cm) 5 AVM	4 AVM anterior circulation 1 AVM posterior circulation 1 AVM perforators	(1) 4 patients	1
Renieri et al., 2015 (28)	3	NAD	Superficial (cortical) (3)	I 2 patients II 1 patient	Superficial 3	M (NAD) (< 3 cm) 3 AVM	2 AVM anterior circulation 1 AVM posterior circulation	(1) 3 patients	None
Kessler et al., 2011 (17)	5	4	Deep (3) Superficial (cortical) (2)	III 3 patients IV 2 patients	Deep 4 Superficial 1	M (2.7 cm) (<3cm) 3 AVM	4 AVM anterior circulation 1 AVM posterior circulation	(1) 5 patients	1

***M:** Mean, **NAD:** not detected.*

Table IV: Summary of the Endovascular Techniques Applied

Studies	Combined transarterial & transvenous embolization	Single transvenous embolization	Venous balloon assist navigation	Arterial in flow control and complementary techniques	Cooker pressure technique (Coiling the draining vein)	Access vein route
De Sousa et al., 2020 (7)	40	17	None	14 Arterial feeders had temporary balloon occlusion (Local HTN)	17	Not mentioned
He et al., 2019 (12)	None	19	None	19 Arterial feeders had temporary Balloon occlusion & liquid embolization (Local HTN)	19	*Straight sinus in 9 cases *Cortical veins via the superior sagittal sinus in 6 cases *Cortical veins via the transverse sinus in 4 cases
Koyanagi et al., 2020 (18)	None	51 (1 Patient required 2 sessions)	8	None	50	*Straight sinus (Basal vein of Rosenthal & Internal cerebral vein) in 30 cases *Cortical veins via the superior sagittal sinus in18 cases *Cavernous sinus via inferior petrosal sinus in 2 cases
Viana et al., 2017 (33)	4	8	3	1 Modified pressure cooker technique	None	Not mentioned
Consoli et al., 2013 (5)	3	2	None	1 Arterial feeder had temporary Balloon occlusion (Local HTN)	None	*Straight sinus (Basal vein of rosthental & superior choroidal vein) in 4 cases *Superior petrous sinus in 1 case
Renieri et al., 2015 (28)	None	3	None	None	None	*Cortical vein through superior sagittal sinus in 3 cases
Kessler et al., 2011 (17)	1	4	None	None	1	*Straight sinus (Internal cerebral vein) in 3 cases *Superior petrous sinus (pontine vein) in 1 case *Transverse sinus (vein of Labbe) in 1 case

to achieve, mostly due to the challenging navigation in multiple small arterial feeders and achieving deep and complete Onyx penetration of the plexiform nidus with multiple arteriovenous shunts. Furthermore, arterial occlusion without obliteration of the venous outlet of BAVMs can lead to recurrence (8,12,13). A recent review and meta-analysis reported a total occlusion rate of only 30% with significant morbidity rates and poor clinical outcomes (8).

The current meta-analysis revealed that TVE had a 93% immediate endovascular total occlusion rate, a 90.9% good functional outcome rate, and a 10.5% overall technical complication rate. Moreover, technical complications, which resulted from microcatheter navigation, were documented in only three patients, whereas technical failure was documented in only four patients. Additionally, the single embolized draining vein may, in turn, induce the occlusion of many shunts in the nidus (28), even in patients who did not achieve immediate angiographic occlusion. This was documented in two cases at the 6-month follow-up (12,33).

Selection of Cases for TVE

Understanding the angioarchitecture and characteristics of the BAVMs is imperative in the selection of cases for TVE. Most BAVMs included were 1) small (nidus size was <3 cm), 2) had a single draining vein, and 3) had deep venous drainage (Table II). Large BAVMs mostly have large draining veins, which are more challenging to occlude without reflux. The presence of multiple venous outflows is an obstacle for the retrograde diffusion of embolizing liquid material to all the shunts from

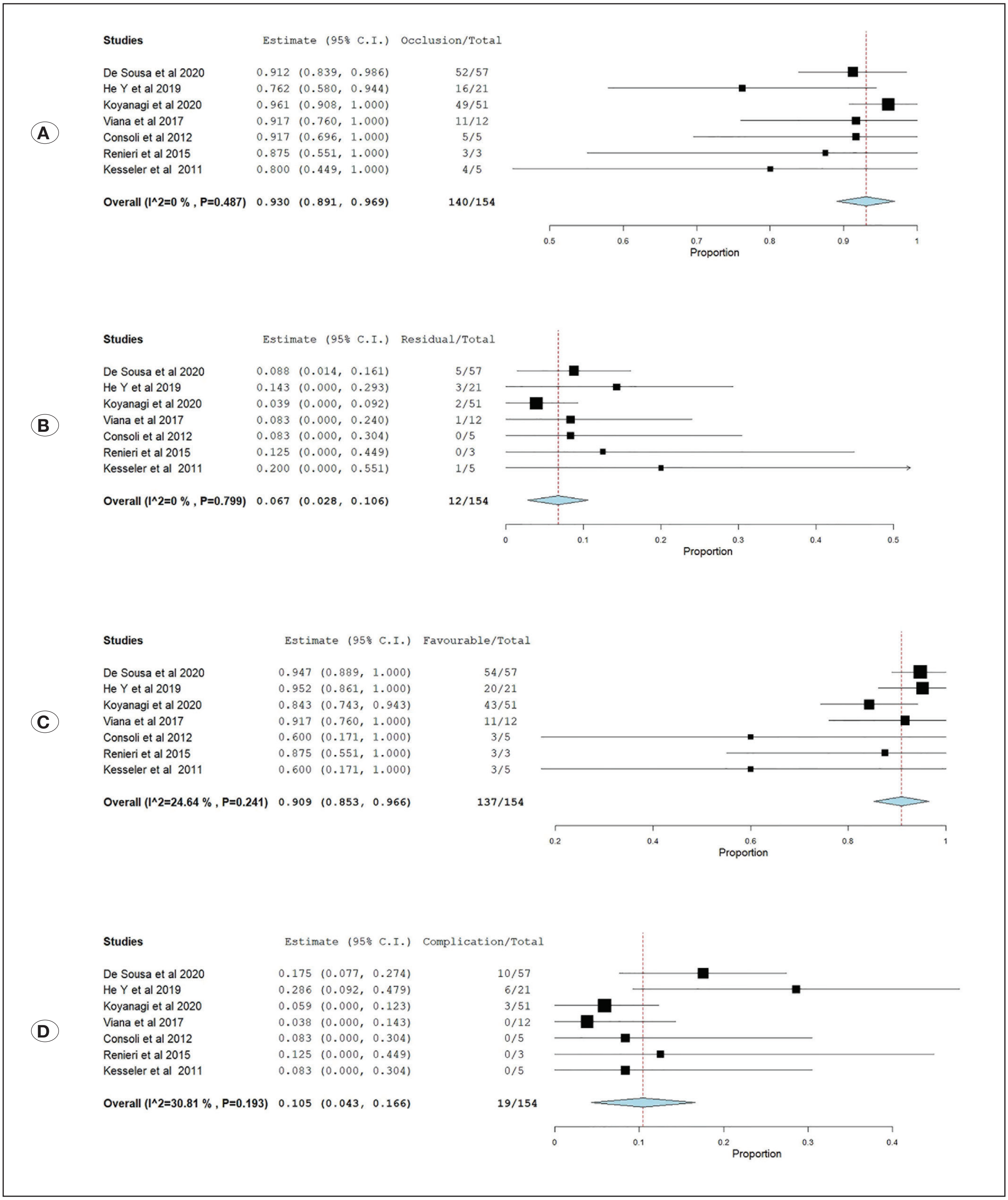

Figure 2: Forest plot for **A)** the primary occlusion, **B)** residual, **C)** favorable functional outcomes, and **D)** complication rates across the studies.

Table V: Summarizing the AVMs Characteristics Associated with ICH and the Time of ICH Occurrence

AVMs characteristics	Number of patients developed complications
Spetzler-Martin grade	
I–II –III	12
IV–V	2
Not mentioned	5
Size	
<3 cm	8
>3 cm	6
Not mentioned	5
Location	
Superficial	8
Deep	9
Not mentioned	2
Pattern of venous drainage	
Superficial	5
Deep	8
Superficial and deep	1
Not mentioned	5
Timing of ICH	
Intraprocedural	6
With 24 hours	4
After 24 hours	3
Not mentioned	6

one vein to another, which may be hazardous (18,29). BAVMs with deep venous draining veins are much easier to access than cortical veins due to their straightforward course and relatively lesser angulation (33).

ICH and TVE

ICH following TVE developed in 18 patients is summarized in Table V. In most of the cases included in this study, induction of relative systolic hypotension for 24 h to prevent ICH and postprocedural computed tomography were performed to rapidly identify and manage any rupture. Koyanagi M et al., He Y et al., and De Souza et al., (7,12,18) suggested several possible reasons other than perforation of cerebral vessels during microcatheter navigation. First, in cases with a large nidus, it is more difficult to achieve complete occlusion for all arterial feeders, and small hidden residuals might be undetected. Second, with multiple draining veins, retrograde nidus embolization through one vein may cause undesired premature occlusion of another draining vein before its complete occlusion and subsequent increase in intranidal pressure. Third, in cases of delayed postoperative ICH, edema, and hemorrhage can occur secondary to impaired cerebral vasoreactivity of the perinodal tissues after excluding the artery–vein shunt. Lastly, other possible high-risk factors include previous rupture, high-grade BAVMs, and deep location with insufficient enough brain tissue and ventricles, and a higher risk of IVH.

TVE and Other Complementary Techniques

In this review, TVE was accomplished with the aid of other endovascular techniques (Table IV). Proximal coil embolization of the draining vein (pressure cooker technique) or balloon-guided navigation was utilized in most of the cases. The transarterial approach was still observed in a significant number of cases that underwent TVE. Combined TAE and TVE were performed in 48 patients. Arterial inflow control during TVE using a balloon or EVOH polymer embolization or modified pressure cooker technique was utilized in 35 patients. Previous sessions of TAE were reported in 44 patients. These numbers highlight the complementary role of TAE to TVE. Similarly, the transvenous approach has been reported to aid the TAE of BAVMs (14).

Limitations and Other Reviews

Previous reviews concerning TVE for BAVMs revealed results almost similar to those reported here. Nonetheless, some limitations were present besides data bias and statistical heterogeneity that could affect any review or meta-analysis. They suffer of methodological limitations of the included studies. Most of the included studies were retrospective in nature, had a small sample size (even case reports were included), and two studies involved cases not treated by transvenous approach, (two studies), which did not report specific TVE outcomes (3,9,21).

The current study did overcome some of these limitations, although case reports were excluded, and all included studies had a relatively larger sample size that focused on TVE alone with more details on its technical aspects and complications. However, most of the included studies were retrospective case series, which are prone to probable selection bias. Finally, the transvenous embolization is mainly carried out in experienced high-volume centers by highly experienced interventionists, which explains the relatively excellent results.

CONCLUSION

Our results suggest that TVE for BAVMs was generally safe and effective in certain selected patients and experienced high-volume centers. However, randomized trials with longer follow-up durations are needed to consolidate these findings. The role of the transarterial approach in prior embolization to TVE or combined embolization or control of arterial inflow during TVE cannot be separated. More studies regarding the complementary role of TAE to TVE as a definitive endovascular treatment for BAVMs need to be conducted.

AUTHORSHIP CONTRIBUTION

Study conception and design: MAD, HE

Data collection: MAD, BIA

Analysis and interpretation of results: MAD, HE

Draft manuscript preparation: MAD, BIA, HE, WM

Critical revision of the article: MAD, BIA, AEE

Other (study supervision, fundings, materials, etc...): MAD

All authors (MAD, WM, HE, AEE, BIA) reviewed the results and approved the final version of the manuscript.

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