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Endovascular treatment of infectious intracranial aneurysms: A single-center experience

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Abstract:

INTRODUCTION: Infectious intracranial aneurysms (IIAs), a notable complication of infective endocarditis (IE), pose significant clinical challenges. This study delineates the outcomes, management strategies, and clinical manifestations of IIAs, drawing from a single-center's experience.

METHODS: We conducted a retrospective observational analysis at our institution, focusing on patients diagnosed with IE between 2016 and 2022 who were also found to have IIAs. Data analysis was performed utilizing SAS statistical software alongside Microsoft Excel to execute descriptive statistical operations.

RESULTS: Among 862 IE patients, 25 (2.9%) were diagnosed with IIAs, totaling 41 mycotic aneurysms. Of these, 18 patients had a single aneurysm, while 7 had multiple. The cohort's median age was 45 years, with an interquartile range of 27–65 years, and a predominance of male patients (68.3%). Ischemic and hemorrhagic strokes were observed in 58.6% and 87.8% of the cases, respectively. Ruptured IIAs were noted in 58.5% of instances, with the remainder unruptured. The average diameter of ruptured IIAs was 3.3 mm, compared to 2.1 mm for unruptured aneurysms, although this difference was not statistically significant ($P = 0.324$). The most frequent IIA locations were the distal segments of the posterior and middle cerebral arteries. Patients with ruptured IIAs experienced higher in-hospital mortality rates (29.1%) relative to those with unruptured IIAs (11.7%). Treatment was administered to 58.3% of ruptured IIAs, with no interventions for unruptured aneurysms ($P = 0.001$). Treatment modalities included surgical resection, n-butyl cyanoacrylate, coils, and Onyx embolization. The treated ruptured IIAs had an average size of 4.4 mm, versus 2.0 mm for untreated aneurysms. Among those treated, the majority were either discharged home (21.4%) or to other facilities (78.6%), with no in-hospital mortalities reported in this group.

CONCLUSION: The findings suggest that endovascular treatment is a viable and effective option for managing ruptured IIAs, with decisions tailored to individual patient comorbidities. Further multicenter studies are recommended to corroborate these findings and refine treatment strategies for IIAs associated with infective endocarditis.

Keywords:

Drug abuse, hemorrhagic stroke, infective aneurysms, infective endocarditis, ischemic stroke, mycotic aneurysms, stroke in young

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Introduction

Intracranial infectious aneurysms (IIAs), commonly referred to as mycotic aneurysms, are a frequent sequelae of infective endocarditis (IE).[1] Approximately 65% of patients with IIAs also have IE, and up to 10% of patients with IE develop IIAs.[2] Moreover, IIAs constitute up to 6.5% of all intracranial aneurysms.[3] They typically arise in the distal segments of the cerebral vasculature, involving the tertiary

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and quaternary branches.[4] This distinct pattern helps differentiate them clinically from berry aneurysms, which are more likely to occur near the base of the brain around the circle of Willis.[5] Although most IIAs result from septic emboli originating from valvular vegetations, other mechanisms such as intravenous drug use, bacteremia, or contiguous infections from sources such as meningitis, orbital cellulitis, or cavernous sinus thrombosis may also lead to their formation.[2]

Clinically, it is crucial to identify IIAs and their etiologies to manage these insidious vascular lesions effectively. A meta-analysis by Petr *et al*. reported that the mortality rate of unruptured IIAs could reach 30%, and the morbidity of ruptured IIAs is approximately 80%.[5] Patients may present with hemorrhagic or ischemic strokes, with common symptoms including headaches, paralysis, vision changes, speech disturbances, seizures, and altered sensorium.[3] A recent meta-analysis by Alawieh *et al*. showed a trend favoring endovascular therapy (EVT) over medical therapy alone in managing IIAs over the last decade, attributed to advancements in neuroendovascular techniques and tools.[1] This approach has been associated with higher treatment success rates and lower mortality.[1] However, despite the favorable trend toward EVT, data on the safety and efficacy of these interventions primarily come from smaller case series and reports, with no randomized controlled trials establishing a standard of care. Moreover, the optimal timing between valvular surgery and aneurysm embolization remains uncertain.[2] In this retrospective analysis, we aim to review current literature and describe various surgical techniques used in our high-volume center, while highlighting the safety and efficacy of these interventions.

Methods

Study design

We conducted a single-center retrospective observational study on patients diagnosed with IE and infectious intracranial aneurysms (IIAs) who presented to Hartford Hospital, a comprehensive stroke center, from August 2016 to October 2022. IE and IIA cases were identified using the International Classification of Diseases, Tenth Revision codes I33, I38, I39, I76, and I72.9, respectively. Among 862 patients identified with IE, 25 patients with 42 IIAs were subsequently identified through this retrospective chart review. The diagnosis of IE was confirmed using the modified Duke criteria.

Study variables

Baseline characteristics, including age and sex, were recorded. We also investigated other cerebral and cardiovascular variables, such as ischemic stroke, intracerebral hemorrhage, valve types, vegetation size (>10 mm or <10 mm), infective organism, anatomy and size of the mycotic aneurysm, location, number of aneurysms, ruptured or nonruptured status, and types of embolic materials used. The study compared various imaging modalities, including computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). All patients with IE underwent treatment with an appropriate course of antibiotics and antifungal regimens. The choice of embolic material was at the discretion of the operating physician, based on their experience and comfort with specific techniques and materials. A ruptured aneurysm was defined as an aneurysm located at the site of a hematoma on imaging, as determined by consensus from multidisciplinary discussions.

Data collection

Demographic data, presenting characteristics, radiographic features of IIAs, and outcome data were extracted from electronic medical records by three independent reviewers. Any disagreements were resolved through consensus discussions.

Outcome measures

The primary outcome measure was in-hospital mortality. Secondary outcomes included rates of re-rupture postembolization, changes in baseline neurological examinations following embolization, and complications postintervention.

Statistical analysis

Descriptive analyses for continuous and categorical variables were performed using Excel. The sensitivity and positive predictive value (PPV) of CTA were calculated from patients with positive conventional angiography results using 2 × 2 tables in Excel.

Clinical trial registry

This work is a retrospective study. No clinical trials were involved.

Results

Main population of IIAs

Among 862 patients with IE identified from our database between August 2016 and October 2022, we found 25 (3.0%) patients with intracranial infectious aneurysms (IIAs), totaling 41 IIAs. Eighteen patients had a single aneurysm, while seven had multiple aneurysms. The median age (interquartile range) of our patients was 45 (27–65) years, with 28 out of 41 (68.3%) being male. Ischemic strokes were present in 24 out of 41 (58.6%) patients, and hemorrhagic strokes in 32 out of 41 (87.8%) patients. Vegetation size exceeded 10 mm in 27 out of 41 (66.0%) patients. Streptococcus was the most prevalent organism in 17 out of 41 (41.5%) patients, followed by

Staphylococcus aureus in 10 out of 41 (24.4%). The mitral and aortic valves were affected in 22 out of 41 (53.7%) and 19 out of 41 (46.3%) patients, respectively [Table 1].

The overall mean size of IIAs was 2.8 mm (range: 0.2–11 mm). Fourteen out of 24 (58.3%) ruptured IIAs were treated, whereas none of the nonruptured IIAs were treated ($P = 0.001$). The mean size of ruptured IIAs was 3.3 mm (range: 0.2–11 mm) versus 2.1 mm (range: 0.8–5 mm) for unruptured IIAs ($P = 0.324$). IIAs most commonly occurred in the distal segments of the posterior and middle cerebral arteries in both groups.

Table 1: Baseline characteristics of the IIAs population (*n*=41)

	n (%)
Age (years), median (IQR)	45 (27–65)
Gender	
Men	28/41 (68.3)
Women	13/41 (31.7)
Number of aneurysms	
Single	18 (72.0)
Multiple	7 (28.0)
Ischemic strokes	24 (58.6)
Hemorrhagic strokes	32 (87.8)
Valve vegetation size (mm)	
>10	27 (66.0)
<10	14 (34.0)
Infective organism	
Streptococcus	17 (41.5)
Staphylococcus	10 (24.4)
Valve affected	
Mitral	22 (53.7)
Aortic	19 (46.3)
Size of IIAs (mm), mean (minimum–maximum)	2.8 (0.2–11)
Ruptured IIAs	24 (58.5)
Unruptured IIAs	17 (41.5)
Overall outcomes	
Home	11 (26.8)
Discharged to rehab	21 (48.8)
In-hospital death	9 (24.4)

IIAs: intracranial infectious aneurysms, IQR: Interquartile range

The in-hospital mortality rate was higher in patients with ruptured aneurysms (29.1%) compared to those with unruptured aneurysms (11.7%), although this was not statistically significant ($P = 0.18$). Similarly, patients with ruptured aneurysms were less likely to be discharged home compared to those with unruptured IIAs (16.7% vs. 41.2%, $P = 0.08$) [Table 2].

Regarding surgical intervention, 14 out of 41 (34.1%) IIAs received treatment, while 27 out of 41 (65.9%) did not. Treatments included surgical resection (1 patient), n-butyl cyanoacrylate (n-BCA) (4 patients), coils (2 patients), and onyx (7 patients) [Figure 1]. The average size of treated ruptured IIAs was 4.4 mm (range: 1–11 mm), significantly larger than untreated IIAs, which averaged 2.0 mm (range: 0.2–9 mm) ($P = 0.002$). Among the treated IIAs, 21.4% of patients were discharged home, and 78.6% were discharged to other facilities. There was no in-hospital mortality observed in the treatment group [Table 3].

Eight out of 41 (19.5%) IIAs were secured before undergoing cardiac valve surgery, with a median of 18 days (range: 10–29 days) between aneurysm securing and valvular surgery. Only 2 out of 41 (4.9%) IIAs were detected postvalvular surgery, based on deteriorating

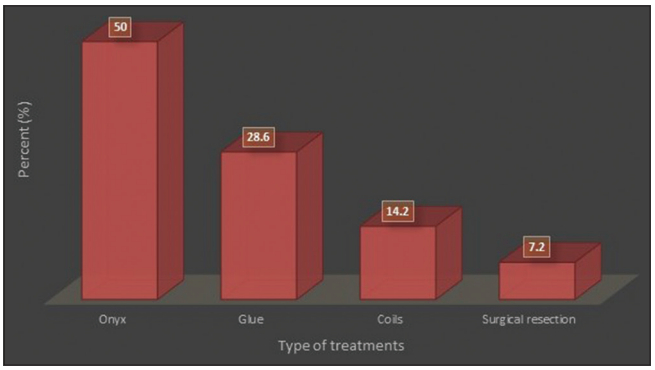

Figure 1: Type of treatment among ruptured infectious intracranial aneurysm population (*n* = 14)

Table 2: Ruptured versus nonruptured IIAs population

	Ruptured IIAs (*n*=24/41; 58.5%)	Nonruptured IIAs (*n*=17/41; 41.5%)	*P*
Age (years), median (IQR)	51.5 (27–69)	33 (28.5–53.5)	0.259
Gender, *n* (%)			
Men	16 (66.7)	11 (64.7)	0.896
Women	8 (33.3)	6 (35.3)	
Treated, *n* (%)	14 (58.3)	0	0.001
Not treated, *n* (%)	10 (41.7)	17 (100.0)	
Average (minimum–maximum) size of IIAs; mm	3.3 (0.2–11)	2.1 (0.8–5)	0.324
Most common location of IIAs	M4=6, P4=5, M2 and A3=3	P4=8 and M4=4	
Outcomes, *n* (%)			
Home	4 (16.7)	7 (41.2)	0.157
Discharged to rehab	13 (54.2)	8 (47.1)	
In-hospital dead	7 (29.1)	2 (11.7)	

IIAs: intracranial infectious aneurysms, IQR: Interquartile range

Table 3: Treated versus nontreated IIAs population

	Treated IIAs (*n*=14; 34.1%)	Un-treated IIAs (*n*=27; 65.9%)	*P*
Age (years), median (IQR)	63.5 (35–74)	33 (27–57)	0.012
Gender, *n* (%)			
Men	12 (85.7)	15 (55.6)	0.053
Women	2 (14.3)	12 (44.4)	
Ruptured, *n* (%)	14 (100)	10 (60.9)	0.001
Nonruptured, *n* (%)	0	17 (39.1)	
Average (minimum–maximum) size of IIAs; mm	4.4 (1–11)	2.0 (0.2–9)	0.002
Most common location of IIAs	P4=4, M4, P3, M3, and M2=2	P4=9, M4=7 and A3=3	
Outcomes, *n* (%)			
Home	3 (21.4)	8 (29.6)	0.080
Discharged to rehab	11 (78.6)	10 (37.0)	
In-hospital death	0	9 (33.3)	

IIAs: intracranial infectious aneurysms, IQR: Interquartile range

neurological examinations, and were treated on day 3 and day 15 postsurgery. Four out of 41 (9.75%) IIAs did not undergo valvular surgery due to not meeting surgical criteria or because surgery was not planned during the same admission.

Sensitivity and positive predictive value of non-invasive computed tomography angiography study

A total of 31 IIAs underwent both a conventional cerebral angiogram and CTA. All 31 IIAs were detected on DSA, while only 12 were identified on CTA. The PPV of CTA was 100%, with a sensitivity of 38.7%.

Outcome measures

Of all IIAs (n = 41), one in four was discharged home, two in four were discharged to a facility, and the in-hospital mortality rate was one in four. No IIAs were found to re-rupture following embolization, and there were no changes in any patient's baseline neurological examination postlembolization. No minor or major complications were observed following any intervention or during the same hospitalization, including access site complications, rebleeding, or symptomatic vasospasm.

Discussion

IIAs are common sequelae of IE in hospitalized patients. Rupture may lead to subarachnoid hemorrhage and/or intraparenchymal hemorrhage which lead to increased morbidity and mortality. This underscores the need for more data on the management of IIAs. Our study investigated 41 IIAs among 25 patients and found that 58.3% of ruptured IIAs were managed with endovascular or surgical techniques while none of the unruptured IIAs were treated as such. Among those IIAs treated, 92.8% were treated with an endovascular approach; 50% underwent Onyx embolization, 28.6% underwent n-BCA embolization, 14.2% underwent coil embolization, and 7.2% underwent surgical intervention. The average size of ruptured and nonruptured IIAs were 3.3 mm and 2.1 mm, respectively. The average size of a ruptured IIA that was treated was 4.4 mm. The overall mortality among all patients was 24.4%. To our knowledge, this is among one of the larger single-center studies evaluating the outcomes, efficacy and safety of various endovascular techniques for the treatment of IIAs.

It is imperative to consider patients with high-risk features who might develop IIAs. In our study, the majority of IIAs were found in young- to middle-aged men (median age 45 years), who comprised 68.3% of patients. This is similar to the male predominance noted in large meta-analyses which were also more common among young to middle-aged men ranging from 18 to 55 years of age.[1-3] According to Alawieh *et al*., the most common risk factor for IIAs is IE.[1] The incidence of IE was noted to be greater among men in our study as well as the reviewed literature.[6] It has been postulated that estrogen has a protective role against endothelial injury and cardiovascular disease which may then contribute to the lower incidence of IE in women.[7,8] In addition, our study also noted a predilection for IE affecting the left side of the heart similarly reported by Desai *et al*.[3] Specifically, the mitral valve was involved in 53.7% of patients with IIAs with vegetation size larger than 10 mm (66.0%). The etiology for the left heart to be affected might be a result of the high-pressure system resulting in turbulent flow and endothelial injury, and the higher oxygen concentration, which is more conducive to bacterial growth.[9] In contrast, intravenous drug use would likely result in right heart vegetations as particles are likely to become trapped in the pulmonary vasculature.[10]

Furthermore, ischemic and hemorrhagic strokes were the most common initial findings at 58.6% and 87.8% respectively. Alawieh *et al*. found that 75% of patients were more likely to present with hemorrhage.[1] However, Serrano *et al*. found that 67.7% of patients were found to have ischemic strokes on admission, whereas 54.8% had

hemorrhage on initial imaging.[4] Perhaps thrombosis occurs more distally resulting in smaller volumes of infarcted tissue, whereas hemorrhage due to a ruptured aneurysm or due to hemorrhagic transformation might result in worse outcomes prompting earlier diagnosis and management.

Currently, there are no guidelines for the management of IIAs due to the small sample size of observational studies and no controlled studies. Options include conservative management with antibiotic therapy, open cranial surgery, EVT, and a combination approach.[11] As EVT continues to evolve, there is a trend away from conservative therapy alone. Ragulojan *et al*. demonstrated that more than half of aneurysms (56.2%) were managed conservatively, resulting in death or ultimately required intervention.[11] Furthermore, Petr *et al*. found that conservative management with antibiotics produced variable results with 50% of patients having resolution or shrinkage of aneurysms and the other half of the patients demonstrating no change or progression of IIAs.[5] A neurosurgical approach may be employed in cases with large hematomas due to the need for evacuation to reduce the consequences of increasing intracranial pressure. Clipping is challenging as the infected aneurysms are friable. Therefore, resection or parent artery occlusion and sacrifice with or without bypass are alternative options for securing an aneurysm.[2] In contrast, an endovascular approach has been gaining favorability.[1,3] This is likely due to availability of microcatheters and microwires with ability to safely access very distal segments of intracranial vasculature. Desai *et al*. analyzed 243 IIAs and compared various endovascular techniques. Unlike our single center study that employed Onyx embolization as the most common technique at 50%, Desai *et al*. found that coiling was the most commonly used technique at 50.4% followed by n-BCA embolization and Onyx embolization at 28.2% and 16.1%, respectively.[3] Coiling is durable and allows for controlled deployment, however, there is risk of aneurysm rupture, coil infection, coil compaction, and recanalization.[4] Although onyx and n-BCA both allow for controlled deployment, n-BCA usage results in virtually instant polymerization which increases the risk of adhering a microcatheter in place inside the vessel.[3]

Our cohort reported an overall mortality rate of approximately one in four IIAs. Similarly, the overall mortality reported in the literature was found to be between 24% and 25%.[1,2] In our single center study, there was a 0% mortality rate among patients who were treated with endovascular or surgical techniques. In contrast, other databases have reported a mortality rate of up to 15%.[2,11] Of those patients who did not undergo endovascular or surgical intervention, death occurred in one of three IIAs. In comparison, other studies have observed a mortality rate of approximately one in three to four patients who only underwent conservative management.[1,11]

Overall, IIAs pose significant risk to patients, and management requires thoughtful input and critical decision-making capabilities. IIAs are often located distally, irregular in shape, and may be in eloquent regions of the cerebral cortex.[3] Therefore, ruptured IIAs may result in devastating outcomes as the mortality of ruptured IIAs approaches 80%.[5] Furthermore, it should be noted that the rupture rate of IIAs has ranged from 2% to 10%.[12] This underscores the necessity of considering intervention for patients with IIAs. There are several variables that may be considered when deciding whether it is prudent to treat a patient's IIA. Our study aligns with Serrano *et al*. and suggests that treating ruptured IIAs is beneficial.[4] In addition, it is reasonable to consider size and location of the aneurysm. IIAs that ruptured were more likely to be larger in average size compared to unruptured IIAs at 4.4 and 2.0 mm, respectively in our cohort. Thus, it may be gleaned that larger aneurysms should be considered for intervention. The decision regarding intervening upon unruptured aneurysms remains challenging. If the IIA is located distally, small in size, and unruptured, it may be reasonable to monitor. However, if an IIA is reachable and if there is a low risk of causing significant neurologic disability, it may be reasonable to offer intervention given the significant risk of mortality.[4] Moreover, the risks versus benefits of intervention should be emphasized to patients and families. Therefore, management and intervention should be considered and selected on a case-by-case basis until more stringent guidelines can be established.

In addition to management techniques regarding IIAs in IE, strategic cardiac valve surgery planning also remains imperative. Standard recommendations are to delay cardiac surgery 4 weeks if patients are treated conservatively and if they remain stable.[1] However, if one is able to embolize and secure IIAs, then that delay between EVT and surgery may be shortened. Our study found that approximately one out of five IIAs was secured prior to cardiac valve surgery. The time interval between EVT and valve surgery was a median of 18 days. In comparison to our study, Serrano *et al*. showed that the time interval between EVT and cardiac valve surgery was a median of 2.5 days.[4] Most IIAs were embolized before surgery as long as the patients were hemodynamically stable.[4] Although the time interval differed between the studies, the literature suggests that securing IIAs will shorten the delay and promotes successful outcomes.[1,4]

Although our study is one of the larger single center cohort studies to our knowledge, multiple factors should be considered when interpreting the data. A major limitation of this study is that it is a retrospective

observational study, and thus guidelines or standard of care cannot be determined. IIAs are each unique and different, and the chosen method of treatment was not standardized. In addition, the data are obtained from a small cohort, thereby yielding low power. Moreover, operator bias cannot be excluded. Furthermore, there is possibility for selection bias that may have impacted our reported mortality. Only some of the IIAs that had ruptured were intervened upon, possibly more stable patients with fewer comorbidities. Despite of such limitations, our study will provide additional valuable insight to the existing literature on management of IIAs.

Conclusion

EVT is overall safe and effective in the management of IIAs and may be considered among patients with ruptured IIAs. Patients who have had their IIAs secured are less likely to experience in-hospital mortality and more likely to achieve favorable outcomes on discharge.

Author contributions

Dr. Patel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Patel, Otite, Mehta; Acquisition of data: Patel; Analysis and Interpretation of data: All authors; Drafting of the initial manuscript: Patel; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: Patel; Supervision: Mehta.

Ethical policy and institutional review board statement

Not applicable due to the retrospective study. A total waiver of consent was granted, as this study involves no direct patient enrollment.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

Patel S, D. had full access to all of the study data and took responsibility for the integrity and accuracy of the data analysis. Part of the study was accepted as "posters presentation" at the SVIN conference, 2023.

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