The Effectiveness of Different Treatment Modalities for Brain Arteriovenous Malformations in Providing a Seizure-Free and Neurological Deficit Free Outcome in Adult Patients: A Systematic Review

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Abstract. An arteriovenous brain malformation is a disorder where there is a tangle of abnormal blood vessels that connect arteries and veins. Proper functioning of blood vessels is vital to the brain's oxygenation but with a brain arteriovenous malformation Â that disrupts oxygenating the brain. Arteriovenous malformations can occur anywhere, but they most commonly occur in the brain and spine. Once diagnosed, surgical treatment options are available to control and stop the disease, such as surgical resection, endovascular embolization, and stereotactic radiosurgery. The objective of this article is to determine the effectiveness of different treatment modalities for brain arteriovenous malformations in providing a seizure-free and neurological deficit free outcome in adult patients. An extensive literature search was conducted using PubMed and PubMed central as our main databases. The articles exploring the association and success rate between different treatment modalities and seizure and neurological-free outcomes were included. A total of 2066 studies were obtained by searching the databases, and after thorough screening, 29 studies were included for the review. This review highlights that microsurgery provides the best seizure control; however, if complete obliteration is achieved with stereotactic radiosurgery, then that offers the best control, and that is something that needs further investigation as there aren't as many studies on it. Moreover, we concluded that further investigations should be done on the combination therapy comprising embolization and stereotactic radiosurgery. It has great potential to provide a large percentage of the patients with this condition to achieve a seizure-free status.

To cite this article
[Nadir, B., Toriola, T., Jamil, M., Gudapati, D. & Khan, S. (2021). The Effectiveness of Different Treatment Modalities for Brain Arteriovenous Malformations in Providing a Seizure-Free and Neurological Deficit Free Outcome in Adult Patients: A Systematic Review. *The Journal of Middle East and North Africa Sciences*, 7(11), 19-34]. (P-ISSN 2412- 9763) - (e-ISSN 2412-8937). www.jomenas.org. **3**

Keywords: Brain avms, microsurgery, stereotactic surgery, endovascular embolization, seizures free outcome (seizures).

1. Introduction:

An arteriovenous brain malformation (AVM) is a disorder where there is a tangle of abnormal blood vessels that connect arteries and veins. Proper functioning of blood vessels is vital to the brain's oxygenation but with an arteriovenous malformation that disrupts oxygenating the brain. They can occur anywhere, but they most commonly occur in the brain and spine; even with that, they are rare and occur in around 1% of the population (Mayo clinic, 2020).

At present, brain arteriovenous malformations' cause is not clear, but usually, most people are born with them, and then they can develop later in life. There is no genetic correlation between the likelihood of developing brain arteriovenous malformations among families. Most commonly, some people with them experience signs and symptoms such as seizures or headaches. Brain arteriovenous malformations cause 3% of seizures in adolescents and 4% of intracerebral hemorrhages, and 9% of subarachnoid hemorrhages in young adults (Al-Shahi & Warlow, 2001). They are usually incidental findings on brain scans for other health issues, such as a patient experiencing brain hemorrhage (Mayo clinic, 2020). However, a third of primary intracerebral hemorrhages in young adults is caused by brain arteriovenous malformations (Al-Shahi & Warlow, 2001).

Once diagnosed, surgical treatment options are available to control and stop the disease, such as surgical resection, endovascular embolization (EVE), and stereotactic radiosurgery (SRS). Primarily, endovascular embolization is used as a primary therapeutic option and is used in combination with either microsurgery or stereotactic radiosurgery (Jordan et al., 2014). The recorded occurrence of complications from endovascular embolization varies from 3%-25% (Jordan et al., 2014; Taylor et al., 2004). Â Several studies have investigated the possible long-term complications after going through endovascular treatment. Respectively, the morbidity and mortality rates vary between 3.8%-14% range (Haw et al., 2005).

Whereas, when looking at seizures, they are the second most common symptom in patients with arteriovenous malformations, and several studies have investigated the long-term effect efficacy of sterotactic radiosurgery in providing seizure control. A study showed that a seizure-free outcome was achieved in 70% of the patients that they investigated, and 15% of patients reported improved seizure control and less frequency after stereotactic radiosurgeryÂ as compared to their pre-surgery status (Ormond et al., 2018).

Therefore, this systematic review aims to determine the effectiveness of different treatment modalities for brain arteriovenous malformations in providing a seizure-free and neurological deficit-free outcome in adult patients.

2. Methods:

2.1. Protocol:

We followed the Preferred Reporting Items for systematic reviews and meta-analysis guidelines (PRISMA) for carrying out our systematic review.

2.2. Data source and Strategy:

We used various databases such as PubMed, PubMed Central, Medline, and web of Science for our data collection. We searched these databases by using keywords and MeSH terms (medical subject heading) like: "Intracranial arteriovenous malformations," "stereotactic radiosurgery," "endovascular embolization," "neurological deficits free outcome," "effectiveness," "complications" and "seizures" separately and in combination to find the appropriate studies.

Also, this search was reviewed for its relevance to the review. At the end of our search, we eliminated duplicate articles and performed a non-automated search on the included studies' reference lists and systematic reviews. We found a total of 2066 articles from the electronic databases.

2.3. The MeSH terms used:

Effectiveness OR efficacy OR successfulness AND treatment modalities OR embolization OR radiotherapy OR surgical resection OR microsurgery OR endovascular embolization OR gamma knife OR conservative management OR combination therapy OR medical treatment AND Brain AVMs OR cavernous malformation OR true AVMs OR hemangioma OR venous malformation

(("Intracranial Arteriovenous Malformations/complications"[Majr] ORÂ "Intracranial Arteriovenous Malformations/drug therapy"[Majr] ORÂ "Intracranial Arteriovenous Malformations/prevention and control"[Majr] ORÂ "Intracranial Arteriovenous Malformations/radiotherapy"[Majr] ORÂ "Intracranial Arteriovenous Malformations/statistics and numerical data"[Majr] ORÂ "Intracranial Arteriovenous Malformations/surgery"[Majr] ORÂ "Intracranial Arteriovenous Malformations/therapy"[Majr])) AND ("Intracranial Arteriovenous Malformations/diagnosis"[Majr] ORÂ "Intracranial Arteriovenous Malformations/pathology"[Majr] AND "Radiosurgery/adverse effects"[Majr] ORÂ "Radiosurgery/therapeutic use"[Majr])

("neurologic manifestations"[MeSH Terms] OR ("neurologic"[All Fields] AND "manifestations"[All Fields]) OR "neurologic manifestations"[All Fields] OR ("neurological"[All Fields] AND "deficit"[All Fields]) OR "neurological deficit"[All Fields]) AND after[All Fields] AND endovascular[All Fields] AND ("embolization, therapeutic"[MeSH Terms] OR ("embolization"[All Fields] AND "therapeutic"[All Fields]) OR "therapeutic embolization"[All Fields] OR "embolization"[All Fields]) AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND avms[All Fields]

("seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields]) AND free[All Fields] AND outcome[All Fields] AND after[All Fields] AND ("radiosurgery"[MeSH Terms] OR "radiosurgery"[All Fields] OR ("stereotactic"[All Fields] AND "radiosurgery"[All Fields]) OR "stereotactic radiosurgery"[All Fields]) AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND avm[All Fields].

2.4. The MeSH terms used:

2.4.1. Inclusion criteria:

There was language restriction; We only included studies in English. RCTs, cross-sectional studies, cohort studies, case-control studies, systematic reviews, traditional reviews were included. We included studies published in the last ten years. We included only adult patients in our study. We included patients who currently have symptoms suffering from the disease such as ICH, seizures, or one-sided weakness and included patients of both genders.

2.4.2. Exclusion criteria:

Grey literature, books, documents, pregnant women, and patients who've already had some sort of treatment for their condition and duplicate studies were excluded.

2.5. Data Extraction:

All titles, abstracts, and full texts were screened by two reviewers independently. The items were extracted from each study included sample size, year of publication, study design, age range, response rate, and study outcome. Other reviewers also evaluated the research papers gathered by one reviewer for accuracy and eligibility. In the case of disparity, conflicts were resolved by a mutual discussion on the study in question.

2.6. Risk of bias assessment:

The following tools assessed the quality of included studies:

Newcastle- Ottawa checklist: observational/ non-randomized controlled trials, Scale for Assessment of Narrative Review Articles checklist (SANRA): traditional review articles, Assessment of multiple systematic reviews checklist (AMSTAR): systematic review and meta-analysis, CARE guidelines: case reports, Cochrane Risk Bias Assessment tool: Clinical trials.

Only those articles that satisfied >70% of the checklist quality parameters were included in the review.

3. Results:

A total of 2066 non-duplicate studies were obtained for possible data collection and analysis by searching through various databases. Once collected, each research article was analyzed, and some were eliminated from inclusion and exclusion criteria based on their titles and abstracts' relevancy. After conducting the initial review process, the remaining papers were filtered again using the inclusion and exclusion criteria. Once completed, the screening process's last step was to assess the full texts using the quality assessment tool. In this process, it was decided that published articles that achieved a 70% benchmark score would be acceptable for use in this systematic review. In total, 70 studies were assessed for quality; however, only 29 of the previously mentioned articles qualified for inclusion in the systematic review.

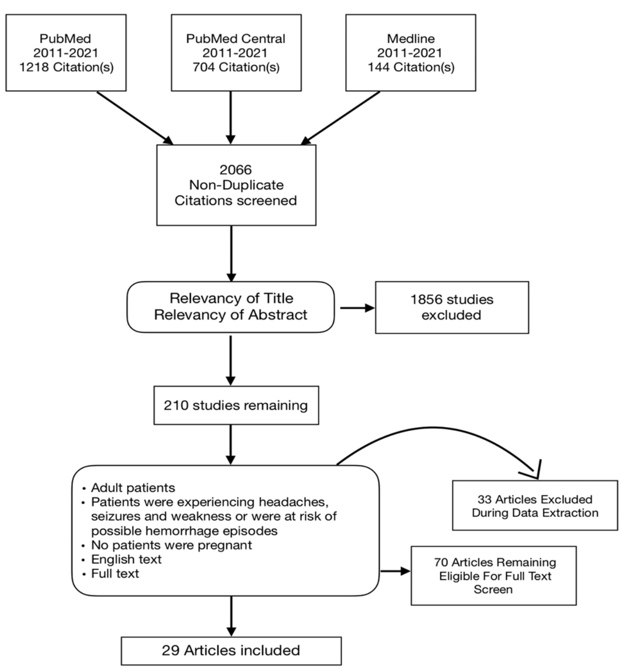

Figure 1. The exclusion and review process are highlighted below

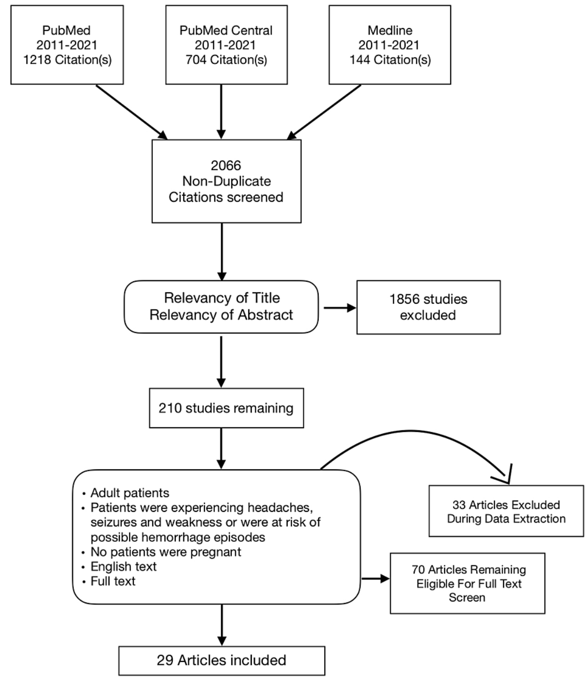

Figure 1. Prisma Flow Diagram

Moreover, table 1 shows the results collected from reviewing the papers selected for this review.

4. Discussion

4.1. Seizures and Brain Arteriovenous Malformations

Arteriovenous malformations present with epilepsy impact a patient's quality of life significantly. However, the primary treatment aim for AVMs is hemorrhage prevention; control of seizures should also be considered primary treatment management. There are many hemodynamic characteristics of AVMs that have been identified to correlate with the presentation of seizures. Such characteristics are as follows; venous outflow obstruction increased AVM flow or located in the frontotemporal location. Although, the eliptogenic nature of brain AVMs is not fully understood. Many theories have been out that include ischemia of the adjacent brain tissue from this "steal" phenomenon, gliosis from the hemosiderin leakage, and subclinical hemorrhage. Another study indicated that abnormal electrophysiological properties of neurons surrounding the AVM and iron-induced free radical damage take part in seizure pathogenesis.

Table 1: Summary of Articles Discussed on Brain AVMs and the Different Treatment Modalities and Their Effectiveness in Providing a Seizure-Free and Neurological Deficit Free Outcome

Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Jordan et al., (2014)	2014	A longitudinal prospective study	71	To determine the predictive factors of neurological deficit after endovascular Treatment of brain AVMs	Endovascular Embolization	The study found the neurological deficit's predictive factors as the partial obstruction of drainage veins, AVMs smaller than 3 cm, intranidal aneurysms, a positive result of the Propofol test, faulty hemodynamic control, and extensive devascularization.
Taylor et al., (2004)	2004	A prospective study	201	The authors of this study viewed pre-op embolization as a useful adjunct in brain AVMs' surgical management. Hence, they are investigating the rate of significant complications in patients undergoing this procedure.	Endovascular Embolization	Although pre-op embolization can reduce the risk of hemorrhage, the risks of this procedure are not insignificant and should be considered properly before undergoing this.
Haw et al., (2005)	2005	Systematic review	513	to determine the mortality and morbidity rates while using EVE and determining factors that may lead to post-procedure complications.	Endovascular Embolization	EVE is associated with low rates of mortality and morbidity in the treatment of brain AVMs.
Ormond et al., (2018)	2018	Retrospective review	155	To assess the seizure-free outcome post SRS and identify the prognostic factors associated with achieving this status.	SRS	Found a positive correlation with SRS and seizure-free outcomes and better seizure control in the patients and found long-term freedom from taking anti-epileptic medication.
Soldozy et al., (2020)	2020	Systematic review	-	To assess the multimodality treatments for epilepsy caused by brain AVMs	SRS, microsurgery, endovascular embolization	It is found that interventional therapy is an effective and safe way of treating epilepsy caused by brain AVMs compared to the stand-alone medical therapy for this, which only provides low to moderate control.

Table 1: Summary of Articles Discussed on Brain AVMs and the Different Treatment Modalities and Their Effectiveness in Providing a Seizure-Free and Neurological Deficit Free Outcome

Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Schäuble et al., (2004)	2004		65	To assess the effects of SRS on patients with brain AVMs and assess the outcomes.	SRS	Sterotactic radiosurgery provides excellent control of seizures post-op, and in the majority of the cases, provides a seizure-free outcome.
Weller et al., (2018)	2018	retrospective review	204	To determine seizure outcomes in patients receiving SRS	SRS	effective control of seizures post-op and seizure freedom.
Baranoski et al., (2014)	2013	meta-analysis	1157	to determine whichever treatment modality selected provides seizure freedom and compare the effectiveness between the modalities.	SRS	In general, microsurgery provides the best seizure freedom; however, it provides the greatest seizure freedom if SRS achieves complete obliteration.
Ding et al., (2015)	2015	case-control study	1400	To determine the SRS outcomes for temporal lobe AVMs and to define post-radiosurgery AVM seizure outcomes.	SRS	The authors found that SRS is an effective treatment in managing Temporal lobe AVMs. They also concluded that in patients with temporal lobe AVM-associated seizures, radiosurgery had protective effects.
Josephson et al., (2011)	2012	a prospective observational population-based study	1862	To compare the risk of epileptic seizures in adults during conservative management or following invasive treatment for a brain arteriovenous malformation (AVM).	conservative vs. interventional therapy	In this observational study, there was no difference in the 5-year risk of seizures with AVM treatment or conservative management, irrespective of whether the AVM had presented with hemorrhage or epileptic seizures.

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Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Derdeyn et al., (2017)	2017	review	-	This review aims to review the current data and make suggestions for the management of brain AVMs.	evaluating all treatment modalities	more research needs to be done to find out the effectiveness of the different treatment modalities and their outcomes
Davidson & Morgan, (2010)	2010	prospective observational population-based study	640	To evaluate the risks associated with surgery, including cases excluded from surgery because of the high surgical risk.	surgical resection	The results suggest that it is reasonable to offer surgery as a preferred treatment option for Spetzler-Martin grade 1 to 2 AVMs.
van Beijnum et al., (2011)	2011	Systematic review & meta-analysis	13699	To assess rates of complications and complete obliteration of brain AVMs after interventional treatment	SRS, microsurgery, endovascular embolization	Treatment of brain AVMs has got considerable risk, such as radiation effects after SRS. Still, more randomized trials need to be conducted to further evaluate as there is not enough data.
Starke et al., (2013)	2013	review	1012	The authors investigated the outcomes of Â Gamma Knife radiosurgery for brain AVMs and they intended to create a scale to predict long-term outcomes.	SRS	Gamma Knife radiosurgery can help in achieving long-term AVM obliteration and neurological preservation predictably based on patient and AVM characteristics.
Mamalui-Hunter et al., (2011)	2011	clinical article	-	To identify if pre-op adjunct use of endovascular liquid embolic agents will reduce Gamma Knife stereotactic surgery's effectiveness in obliterating arteriovenous brain malformations (AVMs).	SRS & EVE	It was found that because of high-energy (60) Co beam, there was negligible dose-reductionby the AVM embolization material for both NBCA and EVOH.

Table 1: Summary of Articles Discussed on Brain AVMs and the Different Treatment Modalities and Their Effectiveness in Providing a Seizure-Free and Neurological Deficit Free Outcome

Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Pandey et al., (2012)	2012	Systematic review	-	To assess the multimodality treatments and outcomes for SM grade I-II brain AVMs	SRS, microsurgery, endovascular embolization	A combination of the treatment modalities seems to provide the best seizure outcome in the SM grade I-II AVMs.
Wang et al., (2013)	2013	Retrospective study	164	To compare seizure control after surgical resection or radiosurgery for AVMs.	Surgical resection & SRS.	Through the study, it was found that surgical resection results in a better rate of seizure control as compared to radiosurgery for patients who present with seizures. However, in patients without presenting seizures, surgical resection increased the risk of new-onset seizures compared to radiosurgery, but primarily within the early posttreatment period.
Blackburn et al., (2011)	2011	Retrospective study (case series)	21	An alternative treatment strategy is suggested where SRS follows endovascular embolization. This study examines the experience at Washington University in St. Louis with Embo/SRS for large AVMs.	EVE followed by SRS	SRS following Staged endovascular can be an effective means of treating large AVMs.
Simon et al., (2004)	2004	clinical trial	27	Endovascular treatment with cyanoacrylate embolization is an option when complete obliteration of the nidus of an intracranial AVM. To evaluate the rates of initial success and permanent cure of this treatment in a Chinese population.	Endovascular Embolization	The overall initial cure rate of the AVMs with cyanoacrylate was 22%. Initial angiography of complete embolization indicated a permanent cure in these patients.

Table 1: Summary of Articles Discussed on Brain AVMs and the Different Treatment Modalities and Their Effectiveness in Providing a Seizure-Free and Neurological Deficit Free Outcome

Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Durst et al., (2015)	2015	article	12	to assess the effectiveness of using an endovascular approach to brain AVM treatment using Onyx, which may allow for a complete angiographic obliteration in a single treatment session.	Endovascular Embolization	Complete angiographic obliteration was achieved in 83% of patients after a single treatment. Morbidity was at 8%, as was mortality. The "reverse plug then push" technique allows for more rapid injection of Onyx due to the formation of a well-controlled plug before treatment, mitigating the risk of catheter entrapment by Onyx reflux. With further refinement, this technique may present a viable curative option for the treatment of select brain AVM.
Asadi et al., (2016)	2016	Retrospective study	199	To identify factors influencing outcome in BAVM patients being treated with endovascular embolization.	Endovascular Embolization	There were 51 further hemorrhagic events during the follow-up period, comprising spontaneous hemorrhage (n = 27) and procedure-related hemorrhage (n = 24). All spontaneous events occurred in previously embolized BAVMs remote from the procedure. Complications included ischemic stroke in 10% of patients, symptomatic hemorrhage in 9.8%, and a mortality rate of 4.7%. It was concluded that brain AVMs could be treated by endovascular techniques or combined with surgery and radiosurgery with an acceptable risk profile.

Table 1: Summary of Articles Discussed on Brain AVMs and the Different Treatment Modalities and Their Effectiveness in Providing a Seizure-Free and Neurological Deficit Free Outcome

Author	Year	Type of Study	No. of patients	Purpose of the study	Intervention studied	Results/ Conclusion
Al-Shahi, (2012)	2012	A prospective observational population-based study	1862	To determine seizure risk with AVM treatment or conservative management	Interventional and conservative therapy	For 229 patients during the 1862 person-years follow up there was no significant difference in the rate of recurrent seizure over five years after brain AVM treatment as compared with the first five years after the presentation of seizure in patients who were treated conservatively when stratified in presentation. For intracerebral hemorrhage, it was 35% versus 26%, with P=0.5; for seizure, it was 67% versus 72%, P=0.6; and for incidental, 21% versus 10%, P=0.4.

SRS: Sterotactic Radiosurgery, EVE: Endovascular Embolization, BAVM: Brain AVM

They included a detailed discussion on how the hemosiderin deposits in the brain tissue surrounding the AVM can inhibit the glutamate and glutamine synthetase's reuptake, hence leading to glutamate-induced cytotoxicity (Kraemer & Awad, 1994). Many investigators have tried to identify the risk factors and possible predictors of seizures in patients with AVMs.

Numerous studies have shown the relationshipÂ between angioarchitecture and location that was found statistically significant. A study demonstrated that the cortical, superficial temporal, cortical feeder, external carotid feeder, and the presence of the middle cerebral artery feeder were stand-alone predictors of seizures secondary to the AVM (Kraemer & Awad, 1994).

With advances in imaging and different quantification methods, various new radiographic attributes of epilepsy caused by AVMs have been identified (Soldozy et al., 2020). There are several available approaches regarding therapeutic management, ranging from conservative management to interventional therapy, such as stereotactic radiosurgery, microsurgery, and endovascular embolization. The interventional therapies can either be used alone or in combination to treat the AVM.

Several studies, especially in microsurgery and stereotactic radiosurgery, evaluate the effectiveness in them providing seizure-free outcomes. The advantage of undergoing microsurgery is that there are superior AVM obliteration rates and quick and effective seizure-free outcomes or effective control.

Additionally, by integrating electrophysiological monitoring during AVM resection, remote or adjacent epileptogenic foci can be identified, leading to extended lesionectomy and effective seizure control (Soldozy et al., 2020).

On the other hand, even though it results in less AVM obliteration and more prolonged seizure freedom, it avoids surgery risks altogether. Usually, it provides better seizure control and seizure-free outcome through different pathways. Several studies show that radiosurgery is very effective in providing a seizure-free outcome that lasts for several years. Furthermore, endovascular embolization is usually used as an adjunct to either microsurgery or radiosurgery in providing an optimal outcome (Soldozy et al., 2020).

4.2. Treatment Modalities

There have been numerous studies that compare the effectiveness of seizure control in AVM patients who have taken different treatment modalities. Recently, there was a retrospective study that was performed at Johns Hopkins University which suggested that a more effective seizure control was achieved with surgical resection as compared to radiosurgery for the AVM, but that the manifestation of the de novo seizures was more likely to occur post-surgical resection as compared to radiosurgery. However, the retrospective study conducted by these investigators analyzed data from complete obliterated AVMs. They found no significant statistical difference in the outcomes of seizures between the different treatment modalities such as embolization, surgical resection, or radiosurgery. The previously mentioned Scottish Intracranial Vascular malformation study also demonstrated that there was a lack of significant evidence in determining the seizure outcomes of different treatment options. Additional studies are needed to further explore whether seizure outcomes in AVM patients are specifically attributable to treatment (Al-Shahi, 2012).

4.3. Stereotactic surgery and seizure control and free outcomes

While evaluating different studies, we found that a study found a clear trend of seizure improvement after undergoing stereotactic surgery in AVM patients, with around 81% of patients initially presenting with seizures and attaining Class I on the Engel Epilepsy Surgery Outcome Scale. There was a significant variation found in the literature regarding the exact rates of improvement in the seizure status. Still, most of the studies indicated that a long-term seizure-free outcome was achieved in numerous patients with brain AVMs who underwent SRS. These study's findings were comparable to those of another study published by the Mayo Clinic in 2000, which had found that 78% of the AVM patients with seizures attained an Engel Class of 1 after their three-year follow post stereotactic surgery (Schäuble et al., 2004).

Another retrospective study published in 2017 that observed seizure outcomes in brain AVM patients following combined therapy for the treatment saw a slightly lower percentage of patients, around 66%, achieving a class 1 on the Engel scale. That same study found and compared different literature and found seven studies that showed rates of seizure-free outcomes post-SRS ranging from 19-85%, and five of these studies demonstrated rates that were greater than 50% (Weller et al., 2018). A systematic review of 24 studies and 1157 patients showed the overall seizure control rate to be around 62.8% within AVM patients treated with SRS, with a significant proportion achieving the seizure-free outcome (85.2%) when the AVM was completely obliterated (Baranoski et al., 2014).

A case series showed that despite knowing the relative variation in the epileptogenic susceptibility between different brain areas, their data didn't show a significant correlation between the chance of achieving Engle class 1 status and the location of the AVM. This was compared to another case-control study where 175 temporal lobe AVM were treated with SRS, with AVM seizure histories and characteristics comparable to the study mentioned above patients. There results also showed no significant correlation between the temporal location and the degree of seizure control (Ding et al., 2015).

The method by which stereotactic radiosurgery reduces seizures or completely provides a seizure-free outcome is not yet fully investigated. One theorized thing is that possibly improved cerebral hemodynamics post radiosurgical obliteration may result in the control of seizures and other adverse effects. This theory is seemingly valid in light of the theories supporting and discussing the steal phenomenon to manifest epilepsy in AVMs. A study conducted in Finland found that the reduction in seizures post radiosurgery didn't rely on the angiographic result; the investigators suggested that control of seizures was attributed to the effects of ionizing radiation (Weller et al., 2018).

However, it has been found that de novo post stereotactic radiosurgery seizures maybe correlate with radiotherapy itself. Studies show a 2-3% risk of permanent neurological deficits caused secondary to injury caused by radiation in patients who undergo SRS. This data is consistent with another study's findings, which showed a rate of 3% de novo seizures consistent at the last follow-up. However, another research showed that 36% of the AVM patients who underwent stereotactic radiosurgery experienced immediate side effects during the two-week post-op period, which included but didn't last longer than two weeks. It was not just limited to the manifestation of seizures (Weller et al., 2018).

Regardless of the evidence that shows improvement in seizure control post SRS for patients with AVMs, several questions remain at hand about these seizures' natural history and progression if no therapy was given. A Scottish Intracranial Vascular Malformation Study (population-based study) had shown no statistical difference between the incidence of de novo seizures and recurrent seizures over the five years between patients with AVMS who received treatment against those who got conservative therapy. As for patients who presented with seizures and had a history of seizures, the study didn't find any statistical difference in the probability of a two-year seizure-free outcome whether therapy was given or not. Hence, this absence of statistical significance was present despite the presenting symptom or the different treatment modality in the intervention group or the complete obliteration of the AVM (Josephson et al., 2011).

4.4. Microsurgery

One of the common approaches to treat a patient with bAVM is surgical resection via craniotomy. The primary objective is a definitive cure. Most do achieve complete obliteration of the AVM, which results in effective post-op seizure control or even a seizure-free outcome; moreover, by completely resecting it, you eliminate the morbidity and mortality associated with bAVM ruptures. Microsurgical resection provides several advantages over the other treatment modalities, such as a high rate of providing complete nidus obliteration, consequently providing immediate elimination of hemorrhage risk, and providing a long-term seizure-free outcome. However, its main disadvantage is invasiveness that results in a greater length of recovery, and more importantly, it has some associated neurological risks (Derdeyn et al., 2017). Many case series have highlighted the safety and efficacy of surgical resection as a treatment for bAVMs (Table 2) (Derdeyn et al., 2017; Davidson & Morgan, 2010).

Table 2: Surgical Outcomes Case Series

Surgical Outcomes Case Series							
Study	**n**	**Year**	**Design**	**Ruptured, %**	**SM Grade**	**Surgical Risk (95% CI), %**	**Obliteration Rate, %**
Davidson & Morgan, (2010)	296	2010	Prospective database	49	I-II	0.7 (0-3)	96.9 Overall
	65	…	…	…	III-IV (No eloquent)	17 (10-28)	…
	168	…	…	…	III-V (Eloquent)	21 (15-28)	…
Fennell et al., (2018)	250	2018	Pooled case series	NR	I	4 (2-7)	NR
	485	…	…	…	II	10 (7-13)	…
	455	…	…	…	III	18 (15-22)	…
	218	…	…	…	IV	31 (25-37)	…
	68	…	…	…	V	37 (26-49)	…
CI indicates confidence interval, NR, not reported and SM, Fennell et al., (2018)							

* Fennell et al., (2018) reported pooled surgical outcomes from seven studies of ruptured and unruptured brain arteriovenous malformations, including the original set for the outcome scale. Two studies were published after 2000, by Davidson and Morgan (Derdeyn et al., 2017; Davidson & Morgan, 2010).
*Reprinted with permission granted by Davidson AS, Morgan MK, Colin P. Derdeyn (Derdeyn et al., 2017; Davidson & Morgan, 2010).

Most of the surgical resection series are single-center, retrospective cohort studies. From these studies, microsurgery seems to be indicated for a specific group of patients with brain AVMs at the lowest risk of preoperative neurological complications. Grading scales have been developed that help predict a patient's outcome after receiving microsurgery treatment; this helps to inform the patient and guide the treating doctor to see the optimal treatment plan for the brain AVM. The Spetzler-Martin (SM) grading scale is the most commonly used classification system that encompasses three anatomic factors: nidus location concerning the surrounding brain tissue, nidus size, and venous pattern drainage enumerate the five bAVM grades (Derdeyn et al., 2017). The SM grading tool is a well-established and reliable tool for estimating the possible irks of the surgical resection using basic imaging data. This grading scale has been proved to be an accurate predictor of the risks of microsurgery. It shows that patients with low-grade brain AVMs (SM grade I & II) have notably less chance of post-op permanent neurological deficits than those with high-grade brain AVMs (Derdeyn et al., 2017).

In 2011, a systematic review and meta-analysis conducted by Beijnum and colleagues reported that AVM obliteration was achieved in 96% of patients, with the rate of 7.4% of patients developing permanent neurological deficits death after microsurgery (van Beijnum et al., 2011). Furthermore, a recent meta-analysis found that microsurgical resection offered superior seizure control and 78% seizure freedom over stereotactic radiosurgery, which provided 63% seizure freedom, and endovascular embolization providing 49% seizure freedom. The highest seizure-free outcome rate was observed in patients who received SRS treatment which had completely obliterated their AVM, which showed 85% seizure freedom. The risk of developing new-onset seizures was lowest in the SRS group compared to the embolization and microsurgery groups. Furthermore, Wang et al. demonstrated that new-onset seizures were more common in patients who underwent microsurgical resection than those who underwent radiosurgery (Derdeyn et al., 2017). Another study showed that 103 surgically treated patients who presented with seizures before surgery demonstrated seizure freedom rates of 77-84% at one-year follow-ups and ten-year follow-ups (Fennell et al., 2018).

obliteration by angiography, the risk of hemorrhage becomes a rare event. When comparing SRS to embolization or microsurgery, the benefits and adverse effects of SRS may not be fully seen for several years after treatment. However, things like radiation-induced necrosis, edema, or cyst formation can develop long after treatment.

Other SRS goals are lessening the seizure frequency in patients experiencing brain AVM-associated epilepsy and preserving or improving neurological function. In patients experiencing bAVM associated epilepsy who underwent SRS and either had a reduction or complete obliteration of the nidus, did achieve seizure-free status, and some achieved less frequency of seizures in the long-term post-op. Preservation of normal neurological function was observed in the vast majority of patients that underwent SRS (Starke et al., 2013). However, prior endovascular embolization can help reduce the size of a large nidus to a suitable size/volume for the SRS and help

Table 3: Radio surgical Outcomes for Brain AVMs (Obliteration Rates)

Radio surgical Outcomes for Unruptured bAVMs							
Study	**n**	**Year**	**Design**	**Follow-up**	**Obliteration rate, %**	**Annual Hemorrhage Rate Before Obliteration, %**	**Permanent Radiation Injury, %**
Ding et al., (2015)	444	2015	Retrospective	86 mo (mean)	62	1.6	2.0
Starke et al., (2013)	2236	2013	Multicenter registry	7 y (median)	64.7	1.1	2.7
Schäuble et al., (2004)	174	2013	Retrospective	64 mo (mean)	78.9	NR	4
bAVMs indicates brain arteriovenous malformations; and NR, not reported							
***Reprinted with permission granted by the authors (Derdeyn et al., 2017).**							

4.5. Stereotactic Radiosurgery

This treatment modality is used to achieve obliteration of brain AVMs in cases that are considered too risky for conventional surgical resection because of anatomic features location or if the patient has other medical problems. Radiosurgery leads to endothelial cell proliferation, concentric vessel wall thickening, and eventual luminal closure (Szeifert et al., 2013). Most of the case series reviewed showed that there was obliteration in 70-80% of brain AVMs after stereotactic radiosurgery as shown below (Table 3) (Derdeyn et al., 2017).

The studies also show that obliteration is commonly achieved two-three years after radiosurgery which is confirmed using angiography. Upon confirmation of

obliterate the high-risk features associated with brain AVM such as intranidal aneurysms. Although this association of the two modalities isn't certain and, if real, it may be related to the possible difficulties in accurately targeting the residual nidus after embolization rather than any impact of the endovascular embolization material the SRS dose (Mamalui-Hunter et al., 2011).

After SRS, some of the noticeable delayed effects include adverse radiation effects; these were observed in the latency period after SRS, symptomatic changes due to the radiation effects in around 10% of patients. However, this risk varies by the brain AVM location, margin dose, and the target volume. The use of corticosteroids has most commonly used to ameliorate the symptomatic radiation effects (Mamalui-Hunter et al., 2011).

It was observed that permanent neurological changes from the radiation occurred in 2% to 3% of patients (Starke et al., 2013). Studies showed that radiation-induced changes could be seen on MRI as hyperintensities around the nidus that have been associated with the eventual nidus obliteration. Observing such MRI features may represent changes in the vascular flow that may indicate progressive brain AVM occlusion. Other delayed effects such as radiation-induced neoplasia or delayed cyst formation are rare but may occur >10 years after SRS.

When considering getting SRS, you have to consider the chance of obliteration and the risk of possible complications caused by the radiation. Several rare but possible post-op complications are brain edema, radiation necrosis, arterial stenosis, delated cyst formation, and organizing hematoma. Two theorized mechanisms by which post-radiosurgery complications can arise are direct radiation injury to the adjacent white matter, which damages the oligodendrocytes following the reactions of the microglia and astrocytes, which may be correlated to brain edema or necrosis. The second mechanism is hemodynamic changes after irradiation (Szeifert et al., 2013). The prevalence of post-radiosurgery complications varies; the occurrence rate of these complications has been reported 30-40% (Derdeyn et al., 2017; Szeifert et al., 2013; 19]. Although, the symptomatic complications rate was recorded to be from 8.1-11.8%. Another study reported long-term complications of GKRS (gamma knife radiosurgery- another form of SRS), such as delayed cyst formation, and found 3.4% of patients developed this. There was also a report of new nidus formation around the obliterated AVM area after GKRS (Pandey et al., 2012).

A retrospective review was performed in patients with brain AVMs presenting with seizures that were treated with radiosurgery. Nineteen case series with data for 997 patients with their seizure outcomes available were evaluated. From this set of patients, 43.8% (437) patients achieve a seizure-free outcome after SRS, and 68.7% (530) patients achieved seizure control (seizure frequency lessened and improved) after SRS. In patients who received SRS and achieved complete obliteration, seizure-free status was achieved in 82% of those patients, and seizure-free status was achieved in 41% of patients with incomplete brain AVM obliteration (Wang et al., 2013).

4.6. Endovascular Embolization

Endovascular embolization is commonly used in the multidisciplinary treatment of brain AVMs. However, it can be used as a stand-alone treatment as well. Preoperative use of embolization is the most common application of its use. Usually, embolization may be curative and used as a stand-alone treatment for completely occluding brain AVMs (Pandey et al., 2012). The detachable tip microcatheter's recent development may further alleviate catheter adhesion and withdrawal risks, which may help this curative strategy. Another use of embolization is an adjunct to surgical resection or radiosurgery. In this case, it can be used to decrease the brain AVM's size or to occlude the ruptured nidal and perinidal aneurysms before the definitive treatment of the remaining brain AVM (Blackburn et al., 2011).

4.7. Embolization as a curative therapy

Several small case series have reported angiographic cures with embolization as a stand-alone therapy. Using cyanoacrylate-based liquid embolic agents, a complete occlusion rate of 20% was reported (Simon et al., 2004). The use of endovascular embolization has increased complete obliteration rates to 51% among all brain AVMs and up to 96% in brain AVMs with simple angiographic features (Durst et al., 2015). The use of detachable tip microcatheters helps facilitate prolonged Onyx infusion, improving the curative rate of embolization. However, embolization as a curative therapy is more suitable for smaller brain AVMs with few arterial feeders and consequentially can achieve complete obliteration (Durst et al., 2015). Furthermore, these characteristics are also familiar to SM grade I and II brain AVMs, which can also be treated with microsurgery. Thus, a comparison must be drawn between the curative rate of embolization against this proven treatment modality. There are concerns about the durability of the embolic materials used and the eight follow-ups required to be certain of a definitive cure. There have been several cases reported of recurrence of brain AVMs after initially achieving complete obliteration (Durst et al., 2015).

4.8. Embolization used as an adjunct to surgery

The primary goal of using embolization before surgical resection is to help reduce the size of the brain AVM and also helping in reducing intraoperative bleeding and helping reducing post-op complications such as normal perfusion pressure breakthrough, which is thought to be related to the chronic low perfusion pressure in the normal brain tissue surrounding the brain AVM (Gutiérrez-González et al., 2012). When an AVM is resected either partially or completely, these areas are prone to normal perfusion pressure, and their function to auto-regulate may be initially impaired. This leads to delayed brain hemorrhage, edema, and seizures, similar to that seen after carotid revascularization procedures. Hence, stages embolization of larger brain AVMs is often undertaken to help reduce the flow to the AVM before its resection (Gutiérrez-González et al., 2012).

The timing of embolization concerning the surgical resection is controversial because there is no good evidence supporting either the immediate pre-surgical or delayed approach. However, in a clinical setting, most doctors prefer to do embolization right before surgery as it reduces the chances of serious complications (Gutiérrez-González et al., 2012). Standard techniques and materials are used, and they include the usage of EVOH, n-butyl cyanoacrylate, polyvinyl alcohol particles, and coils. Frequently, these materials are used in combination as dictated by specific anatomic features of the brain AVM (Starke et al., 2011). Strict management of blood pressure and monitoring changes in the neurological examination should be done in the immediate post embolization period to ensure patient outcomes (Starke et al., 2011).

4.9. Post-Embolization Complications

The most common complications of embolization are ischemic stroke and intracerebral hemorrhage. Thromboembolic complications of catheterization and non-target embolization are a theorized cause of ischemic strokes. Intracerebral hemorrhage may occur from vessel wall injury or rupture of the AVM (Asadi et al., 2016). Microcatheter perforation of the artery feeders may occur as an outcome of access through small tortuous pial arteries, often without a normal vessel wall. However, feeder after aneurysms rarely ruptures as a consequence of mechanical forces related to embolization. Furthermore, most commonly, the AVM may rupture during embolization, withinÂ hours of it, or days after the procedure. There are several reasons for this rupture to occur. Some may be related to the changes in the pressures of flow dynamics in the AVM or the draining vein's accidental closure before eliminating the nidus (Asadi et al., 2016).

Another study evaluated the clinical data and outcomes after 377 procedures on 202 patients. Twenty-nine patients had new clinical deficits after embolization making up 14% of all the patients (Asadi et al., 2016). In a multivariate analysis, the following variables were associated with the deficits: brain AVM diameter >36cm, more than one embolization session, deep venous drainage, and eloquent location. The researchers then developed a scale by weighing these variables and creating a 0-4 point scale. The higher the score, the strength is correlated with the increased risk of neurological deficit. These parameters are similar to those of the SM scale (Derdeyn et al., 2017).

4.10. Treatment modalities and their effectiveness in providing a good seizure outcome

A meta-analysis was done to study the relative rates of seizure-free outcomes after the currently used brain AVM treatment modalities evaluated all the available published data describing the seizure-free outcomes as a goal over the prior 20 years. They included 24 studies with a total of 1157 patients that were analyzed. They found overall the microsurgery group has the best outcome in terms of seizure control with the relative predicted rates of seizure outcome for microsurgery as 78%. As compared to the SRS group with a rate of 62.8% and endovascular embolization at 49.3% (Baranoski et al., 2014). However, it was found that patients who received SRS and achieved complete obliteration of their brain AVM achieved the highest seizure control at 85.2% (Baranoski et al., 2014). It was also observed that the development of new-onset seizures occurred more frequently in patients who underwent endovascular embolization as compared to those who underwent microsurgery , followed by SRS (Baranoski et al., 2014).

Another study investigated the effectiveness of different treatment modalities and the time each different modality took to provide a seizure-free state. They observed a group of 399 patients with brain AVMs, among which some underwent microsurgery, radiosurgery, and endovascular embolization either alone or in combination. The median follow-up time was six years with a range of 3-16.2 years. After microsurgery, radiosurgery, or embolization, the rates of seizure-free outcomes were at 78%, 66%, and 50%, respectively. In the SRS group, the median time to seizure-free status was 20.5 months as compared to the microsurgery group, which achieved seizure-free status in 1.1 months followed by embolization at 8.1 months, respectively (Derdeyn et al., 2017).

In the ARUBA trial, it was seen that intervention appeared to show no benefit on seizure occurrence. However, several studies were published after the ARUBA trial that showed interventional management provided a better outcome in terms of seizure control than just medical management. One of the studies that showed this is a prospective observational study of adults that were newly diagnosed with brain AVMs and annual GP follow-ups, questionnaires and medical records were used to quantify the five-year risk of seizures and chances of achieving a two-year seizure-free status for adults undergoing the interventional therapies in comparison to medical management of the brain AVMs. For 229 patients during the 1862 person-years follow up there was no significant difference in the rate of recurrent seizure over five years after brain AVM treatment as compared with the first five years after the presentation of seizure in patients who were treated conservatively when stratified in presentation (intracerebral hemorrhage, 35% versus 26%; seizure, 67% versus 72%; incidental, 21% versus 10% (Al-Shahi, 2012).

In a retrospective study of 164 patients with brain AVMs that were treated with either radiosurgery or microsurgery, the brain AVM obliteration was predictive of seizure freedom, at last, follow up. It was observed that in patients that didn't present with seizures, 18.4% of them experienced de novo seizures after treatment, for which surgical resection was an independent risk factor (Derdeyn et al., 2017). Another study concluded that Complete bAVM obliteration offered superior seizure-free rates (Baranoski et al., 2014). This data set suggested that the risk of seizures after treatment is lowest when getting surgery and highest after embolization.

5. Limitations

It is important to recognize the limitations of our review. Our results are dependent on the reliability and accuracy of data provided by each of the other studies reviewed and thus may be subjected to reporting bias. Moreover, this systematic review has taken into account several case series, mostly retrospective studies and a single center. Retrospective data is subject to bias and also relies on the quality of the medical record. Moreover, this is a systematic review. Hence, none of the results extracted from the effects of different treatment modalities on seizure outcomes can be compared to a baseline data set. Furthermore, while conducting the systematic review would limit my own bias, having my own set of data to compare it to the others sets of data collected would better enable us to assess the accuracy of the papers being reviewed.

6. Conclusions

After reviewing all the papers and their data, we found that there can be a clear difference in the effectiveness of the treatment modalities in providing a seizure-free outcome. SRS seems to provide the best outcome in terms of seizure freedom, but only when complete obliteration of the brain AVM is achieved compared to the microsurgery, which also provides a good seizure-free outcome as it achieves complete obliteration more frequently. There is a lack of studies and data on embolization effectiveness as a stand-alone therapy for brain AVMs. However, it is the least efficient from the data collected and puts patients at risk of developing several complications. This review highlights that microsurgery provides beat seizure control; however, if complete obliteration is achieved with SRS, that provides the best control. That is something that needs further investigation as there aren't as many studies on it. Moreover, we concluded that further investigations should be done on the combination therapy comprising embolization and SRS. It has great potential to provide a large percentage of the patients with this condition to achieve a seizure-free status.

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Received September 30, 2021; reviewed October 06, 2020; accepted October 17, 2020; published online November 01, 2021