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A single - center retrospective observational study on patients undergoing Encephalo-Duro-Arterio -Myo-Synangiosis in patients with moyamoya disease

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Abstract:

BACKGROUND: Many cases of moyamoya disease are refractory to conventional medical therapy, hence surgical revascularization techniques have emerged as one of the primary choices of treatment. In this study, we present the functional and angiographic outcomes of patients undergoing encephalo-duro-arterio-myo-synangiosis (EDAMS).

METHODS: This is a retrospective observational cohort study, done over 8 years (2012–2020) in a neurological center in Eastern India. Data were retrieved from the hospital's electronic system, recorded in a standard data abstract sheet, and analyzed.

RESULTS: This study included 75 patients, with a male (*n* = 42; 56.0%) preponderance. Majority belonged to the pediatric age group (≤18 years) (*n* = 70; 93.3%); remaining adult population included 5 (6.6%) patients. The most common presenting complaint was that of an ischemic cerebrovascular accident (CVA) (*n* = 57; 76.0%). Symptomatic hemispheres (*n* = 69; 92.0%) were treated and later followed if they had progressed to bilateral disease formation. Preoperative DSA showed 50 (71.4%) to have Suzuki grade 3 type of angiographic findings. Postoperative complications included worsening unilateral hemiparesis 4 (40%), slurring of speech (*n* = 2; 20.0%), hematoma (*n* = 2; 20.0%), and surgical site infection (n = 2; 20.0%). One patient succumbed to his illness on the second postoperative day. A postoperative angiogram showed regression of moyamoya vessels in the majority (*n* = 69; 93.3%) of patients. All (*n* = 74; 100%) had an intensification of transdural vessels; none had a regression. None of the study participants showed an intensification of moyamoya vessels. Many of our patients (83.8%) had a good grade of revascularization (modified Matsushima and Inaba A and B), while 16.2% had low-grade revascularization (grade C). On assessing outcomes using a modified Rankin Score, a large number of our patients had an excellent (*n* = 45, 60%) neurological outcomes.

CONCLUSION: There was a bimodal age distribution with most of them presenting with ischemic CVA. This procedure (EDAMS) had good angiographic (Matsushima and Inaba) and functional (modified Rankin Score) outcomes.

Keywords:

Encephalo-duro-arterio-myo-synangiosis, indirect revascularization, moyamoya disease, puff of smoke

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Introduction

Moyamoya disease (MMD), a rare cause of chronic cerebral vasculopathy, was

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first reported by Takeuchi and Shimizu in 1957.[1] Several years later, in 1969, Suzuki and Takaku coined the term "Moyamoya" for this disease, translated from Japanese to mean "puff of smoke."[2,3] Pathologically, progressive stenosis of the distal (intracranial) portion of the internal carotid artery (ICA) results in the development of small collaterals traversing the basal ganglia and thalamus. Clinically, this presents as either an ischemic (more common in children) or hemorrhagic (more common in adults) stroke, with a characteristic bimodal age distribution, with one peak at 5 years of age, and a second at mid-40 years.[4-6]

MMD is more common in East Asian countries such as Korea and Japan than in the Western hemisphere for reasons unknown. Based on 267 newly diagnosed cases of MMD in Hokkaido, Japan, between 2002 and 2006, Baba *et al*. reported that the incidence and prevalence have increased from 0.94/100,000 to 10.5/100,000. A bimodal peak of the disease occurrence, were seen in studies conducted by Kuriyama *et al*. in Japan (2003), Miao *et al*. in China (2000–2007), Yim *et al*. in Korea (2004–2008), Chen *et al*. in Taiwan (2001–2011), and Uchino *et al*. in Washington (1987–1998).[7-11] These studies also demonstrated an increase in the number of cases for reasons unknown.[7-11] Literature review also suggested that the family members of patients with MMD are at a 30–40 times higher risk of developing MMD than the general population.

The diagnosis of MMD should be considered in children presenting with ischemic cerebrovascular accident (CVA) or transient ischemic attack, and patients with symptoms of headache, neurological deficits, and seizures, some of which are refractory to medical treatment.[12] The diagnosis is made through a 6-vessel digital subtraction angiography (DSA) which shows characteristic findings of narrowing of the distal ICA along with the formation of collateral vessels.[5,6]

Surgical revascularization techniques are mainly of three types – direct, indirect, and combined. There is no consensus at present as to the best type of revascularization procedure.[13-16] Encephalo-duro-arterio-myo-synangiosis (EDAMS), a combination of encephalo-myo-synangiosis and encephalo-duro-arterio-synangiosis (EDAS) was proposed and developed in 1984 by Kinugasa and *et al*.[17,18] It is an indirect bypass procedure that involves placing vascularized structures such as branches of the superficial temporal artery (STA), temporalis muscle, and middle meningeal artery onto the pial surface of the brain to promote angiogenesis. In this procedure, as the name implies, no direct anastomosis is created.[17,18]

In this study, we wish to present the outcomes of patients with MMD who have been treated with EDAMS, in an attempt to shed light upon the efficacy of this procedure, as well as to contribute to the larger discussion surrounding this extremely rare condition.

Methods

Study design and setting

This was a retrospective cohort study done in an advanced neuro medicine facility in Eastern India. The center consists of 195 beds and caters to the needs of both neurosurgical and medical patients.

Participants

Only patients undergoing EDAMS during the study period (2012–2020) were included in the study. Nine patients who were lost to follow-up or could not be contacted over the phone for the clinical outcome score or were denied postoperative radiological investigations were excluded from the study.

Variables

Data of the patients were obtained from the in-patient medical records. The details of history, physical examination, and radiological findings of all patients were recorded on a standard data collection sheet.

Preoperative screening

For the initial diagnosis of a hemorrhagic or an ischemic CVA, each participant underwent a computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. Based on these imaging findings, a six-vessel digital subtraction angiogram (DSA) was done to confirm the diagnosis of MMD and to assess STA and middle cerebral artery (MCA) status. The angiographic findings of these patients were further classified based on the Suzuki staging.[19] MRI perfusion (dynamic susceptibility contrast), (1.5T superconducting MRI from SIEMENS; MAGNETOM Avanto) with acetazolamide was performed to assess preoperative cerebral blood flow. The specifications of this tool are given as follows: time to echo (TE) –32 msec, repetition time (TR) –1520 msec, phase resolution –100, base resolution – 128, slice thickness –5.0 mm, fold of view (FOV) read –230 mm, FOV phase –100.0%, bandwidth –1346, slices –19, distance factor –50, phase director – A>>P, and phase oversampling –0.0%. The acquisition parameters are listed as follows: 2D slices – number of slices (per single slice stack) 1–128, per series – up to 262,144, and slice order – ascending, descending, or interleaved. 3D slabs/partitions – number of 3D partitions per single slab – 4–512; number of 3D slabs (3D volumes) 1–128; acquisition matrix – frequency encoding (true imaging matrix without interpolation and/or oversampling) – 64–1024 (in steps of 64), phase encoding – 32–1024; partial

Fourier imaging – phase partial Fourier – 4/8-1 (steps of 1/8), read partial Fourier – selectable, slice partial Fourier (3D) volumes 6/8-1 (steps of 1/8); rectangular field of view (in phase-encoding direction) – 3%–-100%; averaging mode – number of data acquisitions – 1–31, mode – short-term, long-term (LOTA).

Hospital stay

Each participant was admitted at least a day before the planned surgery for a preanesthetic checkup and hemodynamic stabilization as required. Based on their physiological stability postoperatively, they were monitored/medically stabilized in the intensive care unit and thereafter stepped down to general wards. Single antiplatelet therapy (tablet aspirin 75 mg once daily) and a calcium channel blocker were started for all patients immediate postoperatively, along with rehabilitation therapy and/or speech therapy and/or swallow therapy.

Anesthetic considerations

A thorough clinical and laboratory preoperative evaluation was done for each patient and the following parameters were considered intraoperatively; normotension, normocarbia or slightly raised $EtCO_2$ (40–45 mmHg), and normothermia-to-mild hypothermia.[20-22]

Encephalo-duro-arterio-myosynangiosis – the procedure

The STA and the muscle flap were approximated to the surface of the brain and sutured to the dural edges as proposed and developed by Kinugasa *et al*.[17,18] A frontoparietal temporal craniotomy was made, preserving the middle meningeal artery (MMA), dissected branches of STA, and other dural arteries. Along with the MMA, the dura was opened in both the frontal and temporoparietal areas, forming two flaps with the MMA free-floating in the center. The stripped frontal STA branch was put on the frontal surface, and only the proximal and distal sections of its galeas were sutured to the opening dural edge.

Postoperative evaluation and outcome variables

Each study participant was followed up for at least 6 months with clinical findings and a CT or MRI brain. CT angiogram brain or a DSA and magnetic resonance perfusion scan were done at 6 months to assess regression or halt of the intensification of basal moyamoya vessels, increase in transdural and leptomeningeal collaterals (leading to increased perfusion), and evidence of recurrent strokes. Based on the angiographic findings, these patients were further classified using the Matsushima and Inaba grading to assess the postoperative collateral grading formation.[23] The modified Rankin Scale was used to assess the degree of disability or dependency in everyday activities among these patients at 6 months. Based on this score, the clinical outcomes were categorized as excellent (modified Rankin Scale 0–1), good (modified Rankin Scale 2), average (modified Rankin Scale 3), and poor (modified Rankin Scale 4–5).[24]

Data source and management

Data were retrieved from our hospital's electronic database (in-patient's medical record) and documented in a standard abstract datasheet. Data were entered into a Microsoft Excel sheet (version 16.53; Microsoft 365) and thereafter analyzed and depicted in graphical formats in the results. Patient confidentiality was maintained using unique identifiers and password-protected data entry software with restricted users.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was not determined by the institutional review board/ethics committee review, as the retrospective nature of the study, not demonstrate any information of the patient, where he/she could be identified. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check.

Results

Our study included a total of 75 patients who underwent unilateral and/or bilateral EDAMS for MMD over the 8-year (2012–2020) study period. The majority of these belonged to the pediatric age group (≤18 years) (n = 70; 93.3%); with a mean age of 10.11 (standard deviation [SD]: 2.97) years. The mean age among the adult population (n = 5; 6.7%) was 32.8 (SD: 7.01) years [Figure 1]. There was a male (n = 42; 56.0%) preponderance. The male: female ratio was 1.27:1. Among the pediatric age group, most of them had presented to us with an acute ischemic CVA (n = 54; 77.1%); whereas in the adult population, 2 (40.0%) patients presented with an acute ischemic CVA, 1 (20.0%) patient with hemorrhagic CVA, and 2 (40%) had both an ischemic and hemorrhagic CVA [Figure 1]. Symptomatic hemispheres (n = 69; 92.0%) were treated and later followed if they had progressed to bilateral disease formation.

Age-wise distribution and presentation of these patients have been demonstrated in Figure 2. In this cohort, the majority were from the 9 to 10 years age group and most of them presented with an ischemic CVA. While, in the adult population, two patients (40.0%) had an acute ischemic CVA, and two (40%) had both an ischemic and hemorrhagic CVA.

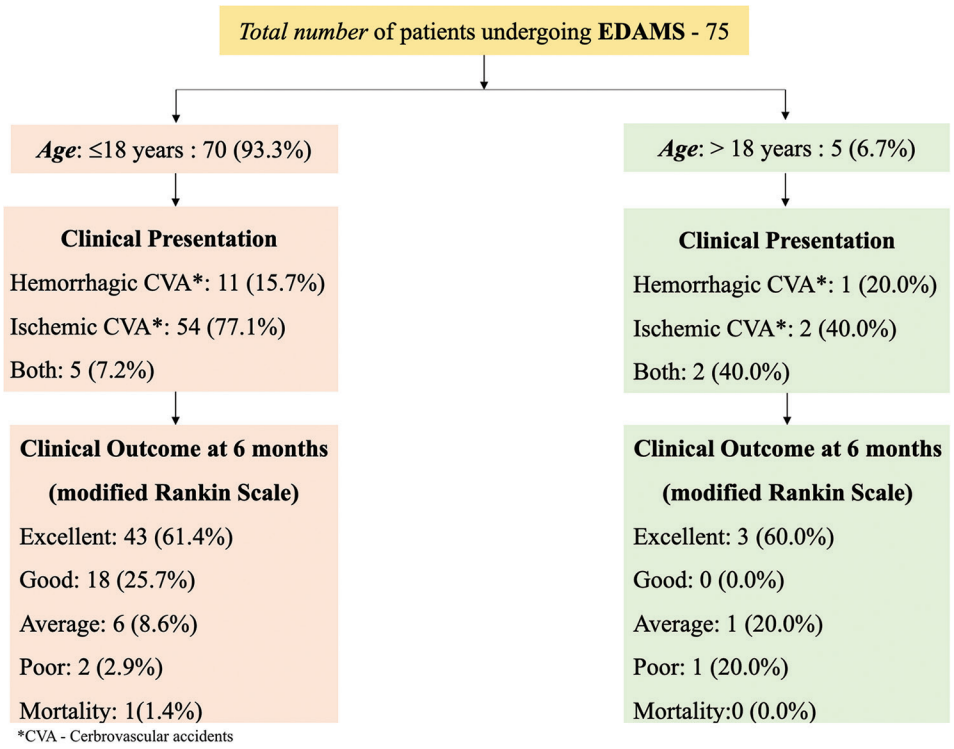

Figure 1: STROBE diagram

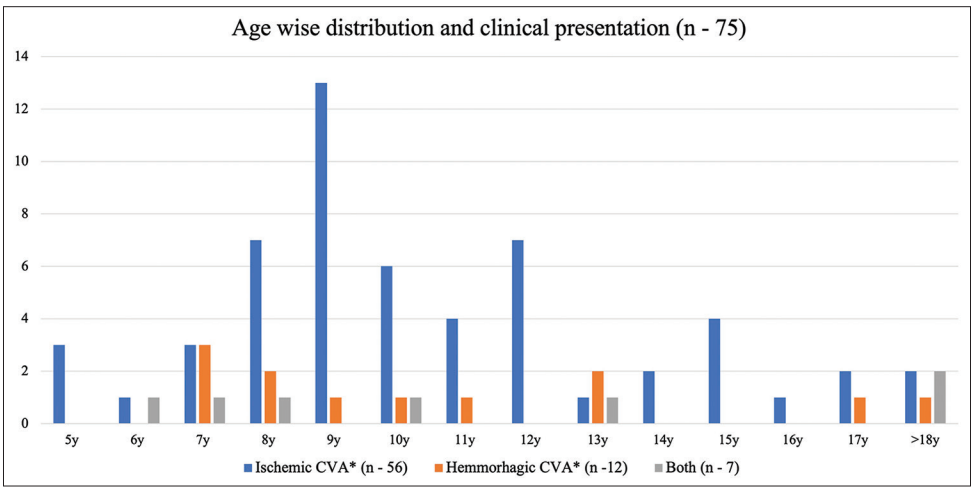

Figure 2: Age-wise distribution and clinical presentation of the disease

Preoperative DSA angiogram was done for all patients. Figure 3 demonstrates these findings based on the Suzuki classification. A substantial part of the study population (n = 50; 71.4%) had a Suzuki grade 3 type of angiographic findings as were in adults.

Postoperative complications within 2 weeks of primary surgery were noted in 10 (13.3%) patients. of these, 4 (40%) patients had worsening unilateral hemiparesis; three-fourths (n = 3) improved partially with supportive care and limb physiotherapy. Other complications included slurring of speech (n = 2; 20.0%), postoperative hematoma (subdural) (n = 2; 20.0%) probably secondary to the primary surgery, and surgical site infection (n = 2; 20.0%) requiring debridement, bone flap removal and long-term antibiotic therapy. Till the time, we followed up on the cases (i. e., at least 6 m) – none reported any surgery-related complications. One patient developed multiple bihemispheric infarcts on the second postoperative day and succumbed to his illness.

A postoperative angiogram was done in 74 cases, which showed regression of moyamoya vessels in the

majority (*n* = 69; 93.3%) of the patients. Five (6.7%) patients had similar findings, such that of the preoperative period. All patients (*n* = 74; 100%) who sustained the procedure well, had an intensification of transdural vessels; none had a regression. None of the study participants showed an intensification of moyamoya vessels.

Based on Matsushima and Inaba classification, age-wise angiographic findings are demonstrated in Figure 4. Matsushima and Inaba grade I findings were noted in the majority (*n* = 57; 77.0%) of the cases. Among the children in the 9–10 years age group, all (*n* = 14; 100%) had Matsushima and Inaba grade I postprocedural findings.

All study participants were followed up for at least 6 months, through telephonic conversation or outdoor visits. Modified Rankin Scores were calculated based on the functional and neurological outcome at the end of 6 months and are depicted in Figure 5. Of the children in the 9–10 years age group, the majority (*n* = 10; 71.4%) had an excellent outcome and the remaining (*n* = 4; 28.6%) had a good outcome. Among the adult age group, Matsushima and Inaba grade I findings were noted in

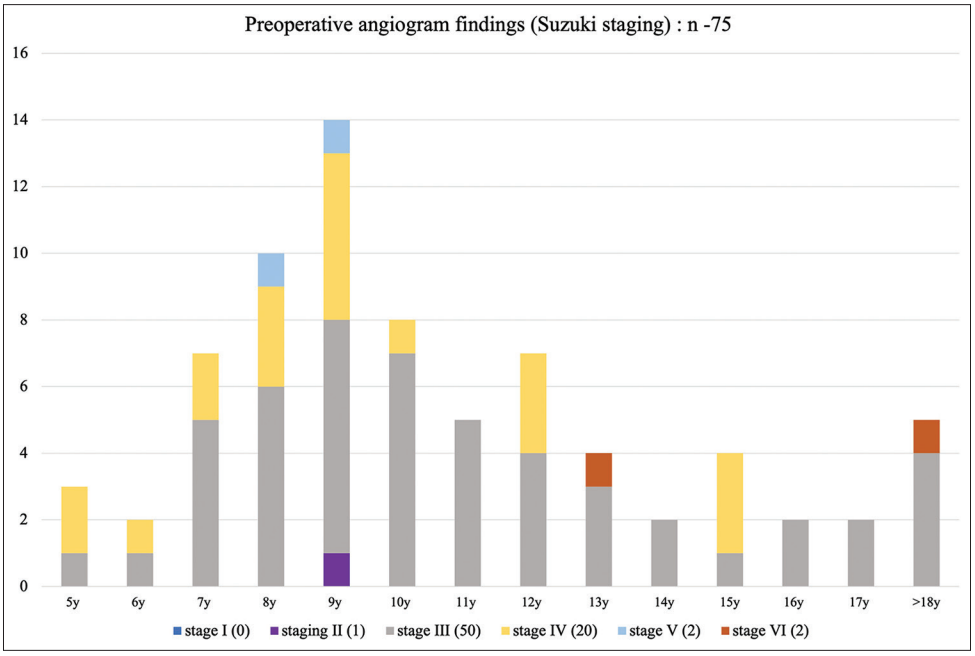

Figure 3: Preoperative angiogram findings based on Suzuki staging (*n* = 75)

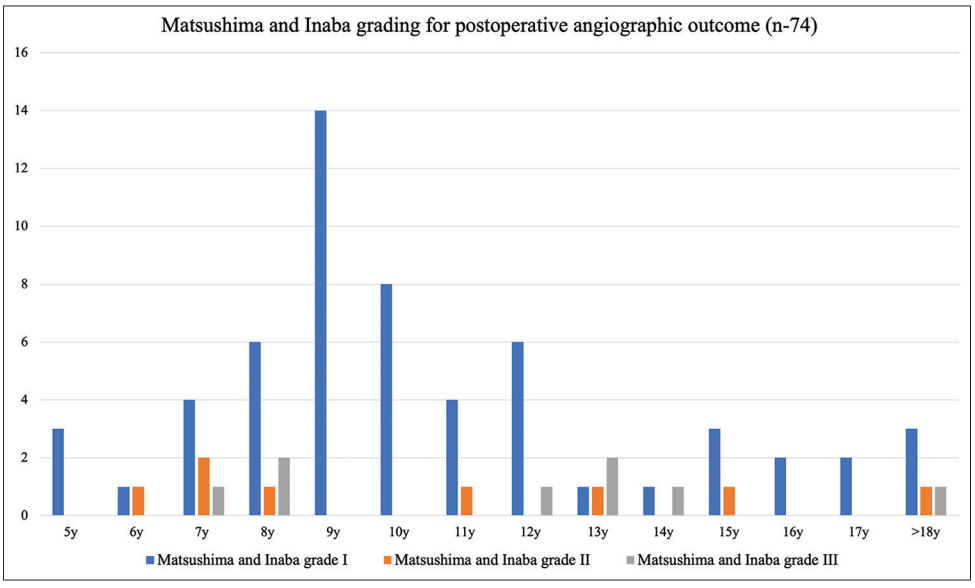

Figure 4: Postoperative angiogram findings based on Matsushima and Inaba classification (*n* = 74)

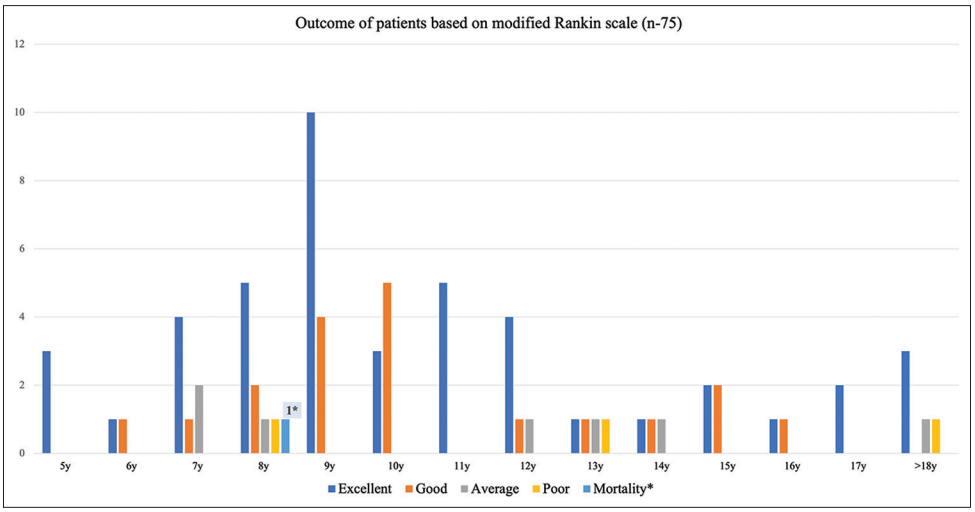

Figure 5: Functional and neurological outcome based on modified Rankin Scoring system (*n* = 74)

three patients and modified Rankin Scores with good outcome was noted in three patients.

Discussion

This is the largest cohort from India assessing the clinical and angiographical outcomes of patients undergoing an EDAMS procedure. Although there are numerous case reports and series from India, the exact prevalence and outcome of patients suffering from this disease are yet unknown. Hence, this study will help in adding data to the already present database of our country.

Suzuki 3 preoperative angiographic grading was noted in approximately two-thirds (66.7%) of the patient population, which was consistent with a study by Qingdong Han on 126 patients, whereas a study by Rosi *et al*., at Boston Children's Hospital on 82 kids had predominantly grade IV disease.[25,26] The majority of our study population had presented to us with an ischemic CVA in the acute phase (<7 days). However, the exact day from the onset of disease to presentation could not be determined due to the retrospective nature of the study. Suzuki postulated six stages of angiographic evolution based on diverse angiographic observations.[19] However, a sequential development from stage 1 to stage 6 has only been documented in a small number of cases, hence the classification's practical utility is yet to be validated.

Revascularization surgery for pediatric MMD has repeatedly proven successful in eradicating ischemic neurological symptoms, regardless of whether direct or indirect bypass surgery is employed. In comparison to direct microanastomosis, Ishikawa *et al*. found that EDAMS may be better suitable for young patients with MMD.[27] Many authors have suggested that combining a direct vascular bypass (STA-MCA or other) with an indirect vascular synangiosis (EDMS, EDAS, and EDAMS) can provide immediate augmentation of cerebral blood flow as well as long-term potentiation through collateral development from the patchwork of fascia graft, muscle, or dura.[17,27-29] Recent studies have also shown that combination surgery is preferable to either direct or indirect surgery alone. Only combination revascularization enhanced cerebrovascular reserve capacity, according to a randomized controlled trial comparing the hemodynamic outcomes of indirect and combined revascularization.[28] Combined surgery (STA-MCA bypass and EDAMS) was conducted in 100 hemispheres and indirect surgery (EDAMS) on 31 sides, according to the literature by Gupta, *et al*. from India.[30] Although there was a trend toward better collaterals in the combined surgery group, the degree of cerebral revascularization was statistically the same in both the combined surgery and indirect surgery groups. On the contrary, Ishikawa *et al*. reported that combined surgery (STA-MCA bypass with EDAMS) for pediatric patients was beneficial in minimizing the incidence of postoperative ischemia episodes when compared to indirect surgery.[27] The angioarchitectural changes influence the clinical outcome following EDAMS surgery. The regression of moyamoya vessels is also quintessential as their thin walls and concomitant microaneurysms, make them more prone to bleeding. When compared to Jiang *et al*., who saw a 51.2% regression rate of moyamoya vessels in their sample of 105 adult patients with hemorrhagic MMD, who all received EDAMS, we saw regression of moyamoya vessels in 92.0% of our participants.[31] This was probably because the majority of our participants belonged to the pediatric age group and had presented with an ischemic CVA.

The grading system devised by Matsushima and Inaba is commonly used to assess the degree of vascular neoangiogenesis.[23] Various authors have reported

varying frequencies of good/poor revascularization. The majority of our patients (n = 66; 88.0%) had good grade revascularization (modified Matsushima and Inaba A and B), while 12.0% (n = 8) had low-grade revascularization (grade C). Jiang *et al*. found identical results, with good (grades A and B) and poor (grade C) collaterals in 85.3 and 14.7% of patients, respectively.[31] According to Bao *et al*., 45% of 109 adult patients (unilateral hemisphere) who had EDAS had grade A collateral circulation, 34% had grade B collateral circulation, and 21% had grade C collateral circulation.[32]

Based on a detailed literature review, each of these participants was initiated on antiplatelet therapy as well as calcium channel blockers till the review visit in the outpatient department at 6 months. The majority of our patients had good functional and neurological outcomes based on the modified Rankin Scoring system. Consistent with other studies on surgical outcomes of patients undergoing EDAMS, our study group had similar or better postoperative outcomes, thereby concluding that EDAMS is safe and beneficial.

Limitations

All patients in this cohort underwent an EDAMS procedure, hence a comparative analysis with other treatment/surgical modalities was not possible. Although there was a positive angiographic outcome at 6 months, the long-term clinical outcome remains unknown. Many patients were lost to follow-up and it was difficult to determine their functional outcome, hence were excluded from the study.

Suggestions for future research

At the very least, a national or region-based study should be conducted to determine the prevalence of this rare disease in our country. The relative efficacy of various surgical procedures has conflicting data; hence approach and treatment protocols need more research for better evidence-based management protocols.

Conclusion

This is an observational report of 75 MMD patients undergoing EDAMS surgery; highlighting the pre-/postoperative outcome. The clinical and angiographic outcomes of EDAMS at our center have been positive. As a result, we believe that indirect revascularization could be one of the most beneficial treatment options in select patients with this rare disorder.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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