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A critical appraisal of bypass surgery in moyamoya disease

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***Abstract*:** Moyamoya disease (MMD) is a complex cerebrovascular disorder about which little is known. Conventionally, revascularization surgery is recommended for patients, despite an absence of conclusive data from adequate clinical trials. Underscoring the uncertainty that exists in treating MMD patients, investigators continue to present data comparing revascularization with conservative or medical management, most of which originates from East Asia where MMD is most prevalent. The purpose of this manuscript is to review contemporary large case series, randomized trials, and recent meta-analyses that compare surgical and medical treatments in adult patients with MMD, and to critically analyze the modern literature in the context of current practice standards. Data from the available literature is limited, but revascularization seems superior to conservative therapy in adult patients presenting with hemorrhage, and in preventing future hemorrhages. Conversely, evidence that surgery is superior to medical therapy is not convincing in adult patients presenting with cerebral ischemia, or for the prevention of future ischemic events. In contrast to East Asian populations, MMD in Europe and in the Americas is predominantly an ischemic disease that presents in adulthood. Adequate multinational trials are warranted.

Keywords: bypass surgery, conservative, moyamoya, medical, revascularization, review

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Introduction

Moyamoya disease (MMD) is a bilateral steno-occlusive disorder of the intracranial terminal internal carotid artery (ICA) and proximal middle cerebral artery (MCA)/anterior cerebral artery (ACA) vessels, with the development of abnormal vascular networks. The condition is considered probable when unilateral, and syndromic when secondary to one of a multitude of known causative disorders from which MMD must be distinguished.[1,2] MMD is characterized pathologically by intimal widening owing to the influx of smooth muscle cells from the media, distortion and disruption of the internal elastic lamina, narrowing of the media, hyperplasia of the invading myocyte cells with deposition of collagen and intimal fibrosis, and gradual progressive arterial luminal compromise.[3,4] Infiltration of macrophages and deposition of lipids may represent secondary phenomena.

MMD is a polygenic disorder believed to be influenced by environmental factors, such as oropharyngeal infections.[4] Phenotypically similar conditions including postvaricella arteriopathy, transient cerebral arteriopathy, and focal cerebral arteriopathy, which may represent a related group of conditions attributable to varicella zoster virus (VZV) infection, raise the possibility of a connection between MMD genetic predisposition and herpetic infection.[5] Familial and sporadic MMD has been convincingly linked to the RNF213 gene on chromosome 17q25.3.[6,7] In Japan, the c.14756G>A variant was present in 95% of familial MMD cases, 79% of sporadic cases, and 2% of controls.[8] In Korea, the c.14756G>A variant was identified in 76% of MMD cases, 35% of intracranial stenoses not diagnosed as MMD, and 0% of controls.[9] In China, the R4810K variant was related to ischemic, and the A4399T variant to hemorrhagic MMD.[10] Also among Chinese,

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Table 1. Suzuki angiographic grading system for MMD.

I	Narrowing of ICA bifurcation.
II	Dilation of MCA and ACA with initiation of neovascular development.
III	Progressive narrowing of ICA and MCA/ACA with prolific neovascularization.
IV	Disappearance of ICA, minimally patent MCA/ACA, and decrease of neovasculature.
V	Disappearance of ICA/MCA/ACA and near loss of neovascular vessels.
VI	Complete loss of anterior circulation and neovascular vessels. Perfusion derived only from VB system and ECA vessels.

ACA, anterior cerebral artery; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; MMD, moyamoya disease; VB, vertebrobasilar.

the RNF213 variant p.R4810K has been associated with posterior cerebral artery (PCA) involvement and earlier age of disease onset.[11] Recently, among European patients with familial (and possibly multigenerational) MMD, a novel gene mutation involving PALD1, which promotes endothelial survival and proliferation, has been identified as a putative synergist to the RNF213 missense susceptibility variants p.A3927T & p.P4033L, thus becoming a new potential contributor to the polygenic constellation of MMD.[12]

MMD is most prevalent in the countries of East Asia, where clinical disease characteristics differ from those observed in Europe and the US.[13,14] In East Asia, prevalence rates of 3–10 cases per 100,000 are at least 10 times greater than those in the US and Europe.[4] East Asian cases, compared with those in the US and Europe, are more frequently familial (10–15% *versus* 1–5%), more equally distributed between males and females (1:1.8 *versus* 1:3.3), are more often pediatric at presentation (major peak ~5 years old *versus* 30–50 years old), and are more commonly hemorrhagic in nature (20–60% *versus* 5–15%).[13,15]

Clinical manifestations of MMD involve ischemic and hemorrhagic processes by various pathophysiological mechanisms. Ischemic mechanisms may involve hypoperfusion,[4] local thrombosis at sites of stenosis,[3] and thromboembolization distal to stenotic vessels.[16] Hemorrhagic mechanisms may involve rupture of fragile parenchymal or pial neovasculature,[3,4] or rupture of aneurysms formed in the neovascular vessels or large basal arteries.[3,4]

Principal radiologic modalities used in the diagnosis and characterization of MMD include cervicocranial six-vessel angiography of bilateral internal/external carotid and vertebral arteries, and cerebral perfusion imaging performed at baseline and following vasodilatory challenge. Angiographic criteria are used to grade disease severity (Table 1),[1,3] characterize intracranial collateral networks, identify extracranial vessels as candidate donors for surgical anastomotic revascularization, and identify coexistent aneurysms.[3] Perfusion imaging may entail computed tomography (CT) perfusion, xenon CT, magnetic resonance perfusion, single-photon emission computed tomography (SPECT) or positron emission tomography (PET), and are used in staging the level of hemodynamic compromise, and hemodynamic reserve following acetazolamide injection.[1,3] Alternate or additional modalities that may contribute to diagnosis and characterization include cerebral magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) [or computed tomography angiography (CTA)], electroencephalography (EEG) with hyperventilation, and transcranial ultrasound.[1,3,4]

Treatment of MMD has mostly entailed surgical revascularization by direct or indirect anastomosis between intracranial ICA and extracranial ECA tributary vessels.[17] By the direct method, an anastomosis is created between the superficial temporal artery (STA) and an M3/M4 tributary of the MCA, and provides immediate perfusion to territories supplied by the involved MCA. The indirect method usually involves placing dissected temporalis muscle over the pial surface of the involved hemisphere to allow gradual (delayed) development of collaterals between the muscle and cortex. Combined direct/indirect techniques may also be performed. To date, there is no consensus regarding which revascularization technique is superior.[17]

Identification of patients at greatest clinical risk, and selection of patients for surgical treatment, has mostly centered around clinical symptomatology, and the corresponding anatomic and physiologic features on angiography, cerebral MRI, and perfusion imaging. However, asymptomatic cases with advanced angiographic disease and severe perfusion defects exist,[18] and opinions vary considerably regarding indications for surgical anastomotic revascularization. Sources have variably advocated surgery for asymptomatic cases with impaired perfusion,[18] for any ischemic symptoms,[19] for symptomatic ischemia plus perfusion impairment,[17] for ischemic cases with only (non-mild) moderate to severe symptoms,[20] and for hemorrhagic cases.[17] According to the Oxford Center for Evidence Based Medicine, data supporting surgery for the treatment of MMD are Level 4, and limited to case series and low-quality case–control studies.[21]

Review articles and editorials from opinion leaders frequently state that surgical management is the required and only effective treatment for MMD, and that (given this foregone conclusion) no randomized trials will likely be performed.[22,23] Interestingly, however, large case series from East Asia continue to compare outcomes between patients treated surgically *versus* medically. The purpose of this article is to review contemporary literature pertaining to the management of adult MMD, with emphasis on large databases comparing clinical outcomes between surgically and medically treated patients, so as to illuminate limitations in the existing data, and to possibly challenge current (mis)perceptions regarding the optimal treatment of MMD patients. This article pertains only to MMD, and not to moyamoya syndrome (MMS) for which therapy may be primarily directed towards the causative condition. It is not the purpose of this article to compare or contrast the different available surgical techniques.

Literature search and selection

We performed an extensive electronic literature search of MEDLINE using PubMed for publications from 1 January 2010 to 1 January 2020 printed in the English language and involving human subjects. Indexing words and phrases used for database queries included “moya-moya”, “moyamoya”, “medical”, “conservative”, “revascularization”, “bypass”, “surgery/surgical”, and “outcome(s)”, entered in various (paired or triad) combinations. Additional manual searches were performed by identifying and reviewing articles referenced in already collected articles as well as those cited by the most recent comprehensive meta-analyses. We selected publications that pertained only to nonsyndromic MMD, contained a minimum total of 75 patients, included a majority of adults (>18 years old), compared medical and surgical therapies, presented data on clinical subgroups (ischemic and hemorrhagic types), and provided analyses on pertinent clinical outcome measures (cerebrovascular and mortality endpoints). For all articles included in this review, the entire printed text was obtained and reviewed in detail. An overview of the selected case-control and randomized trial investigations is provided in Table 2.

Literature review

Surgical case series

In the last decade, reports from various institutions have presented exclusively surgical outcome data with no comparator medical treatment group. In 2009, Stanford University reported a retrospective analysis on 233 adult (389 hemispheres) and 96 pediatric (168 hemispheres) surgically treated patients, the vast majority of whom underwent direct (as opposed to indirect) revascularization: 95.1% (96.6% hemispheres) and 76.2% (67.2% hemispheres), respectively.[38] Whereas adults experienced an ischemic or hemorrhagic complication rate of 5.15% and a 0.86% mortality rate, pediatric patients experienced a 3.13% morbidity and a 1% mortality rate. A 2012 report also from Stanford presented data on 306 adult and 124 pediatric surgical patients (717 total revascularizations), 88.6% of whom underwent direct or combined revascularization.[39] Adverse postoperative events occurred in 9.3% of cases, 62.5% of which were cerebral infarcts and 37.5% of which were hemorrhages, and ultimately resulted in a 1.86% mortality rate. Separate analyses were not performed for the adult and pediatric patients, but substantial trends were noted for greater adverse events in women during both early and later postoperative periods. In 2014, Hokkaido University in Japan reported a retrospective analysis of 108 adult (177 hemispheres) and 128 pediatric (181 hemispheres) surgically treated patients, the majority of whom underwent direct or combined surgical procedures: 92.7% of hemispheres in adults and 90% of hemispheres in pediatric

Table 2. Overview of case-control studies and the randomized trial (JAM)*.

Author (Country) Year	Inclusion criteria	Adults	Total patients Con-Med: Sur(Hemi)	Surgical modality	Operative morbidity	Duration	Endpoint	Findings	Comment
Lee *et al.*[24] (Korea) 2012	Symptomatic ischemia or hemorrhage	100%	142 18:124 (147)	I>C>D	NA	4–5 years	Any vascular event	Fewer events with surgery in ischemic & hemorrhagic groups.	No statistical advantage to surgery in hemorrhagic group.
Duan *et al.*[25] (China) 2012	All MMD patients	100%	802 29:773 (1274)	91% D	5.8%	2 years	Any vascular event	More vascular events in surgical group.	Marked numerical group imbalances and lack/loss of clinical data.
Liu *et al.*[26] (China) 2013	Symptomatic hemorrhage	94%	97 43:54	D>C>I	NA	7 years	Rehemorrhage	Less rehemorrhage and mortality in surgical group.	No data on any ischemic outcomes.
Miyamoto *et al.*[27] (Japan)* 2014	Symptomatic hemorrhage	100%	80 38:42 (84)	(B) D	0%	4 years	Any vascular event	Fewer rehemorrhages in surgical group but no difference in infarctions.	Questionable zero postoperative complication rate.
Noh *et al.*[28] (Korea) 2015	Symptomatic ischemia	100%	104 59:45	I	13.3%	2–5 years	Any vascular event	More infarctions in surgical group. No hemorrhages in both treatment groups.	Group imbalances with worse angiographic grades and perfusion scores in surgical group.
Liu *et al.*[29] (China) 2015	Symptomatic ischemia or hemorrhage	60%	528 122:406	D>I>C	1.5%	3 years	Any vascular event	Fewer hemorrhages, and trend toward fewer infarcts, in surgical group.	Marked group imbalances with more hemorrhagic presentation among con-med group. Substantial loss of data.
Huang *et al.*[30] (China) 2015	Symptomatic hemorrhage	94%	154 28:124 (2 only had aneurysm treated)	D>I>C	7.3%	3 years	Any vascular event	Numerically fewer hemorrhages and infarcts in surgical group.	No statistical benefit from surgery for any outcome.
Kim *et al.*[31] (Korea) 2016	Symptomatic ischemia	100%	441 140:301	98% C	2.6%	4–6 years	Any vascular event	No differences between treatment groups until 10 years when fewer infarcts observed in surgical group.	More advanced disease in con-med group. No surgical advantage in preventing hemorrhages.
Jang *et al.*[32] (Korea) 2017	Symptomatic ischemia or hemorrhage	100%	249 91:158	I>D>C	18.5%	2 years	Any vascular event	Surgery advantageous for hemorrhagic group but not for ischemic group and did not change mortality.	Group imbalances with more hemorrhagic presentation among con-med group.

(Continued)

Table 2. (Continued)

Author (Country) Year	Inclusion criteria	Adults	Total patients Con-Med: Sur(Hemi)	Surgical modality	Operative morbidity	Duration	Endpoint	Findings	Comment
Ge *et al.*[33] (China) 2017	Symptomatic ischemia or hemorrhage, and advanced disease.	100%	82 (75:89)	D	(6.7%)	4–5 years	Any vascular event	No differences observed between treatment groups.	No clinical benefit from surgery despite improved perfusion.
Ge *et al.*[34] (China) 2017	Symptomatic ischemia or hemorrhage, and age >50 years.	100%	87 13:74 (87)	D>I >other	8.1% (6.9%)	3 years	Any vascular event	Numerically fewer events in surgical group.	No statistical differences between groups.
Porras *et al.*[35] (USA) 2018	Idiopathic or syndromic bilateral symptomatic or asymptomatic MMD/MMS	NA	94 (94:90)	I	NA	6 years	Ipsilateral vascular event	No differences in event/survival curves between treatment groups.	Identical event rates in con-med and surgical groups among adults.
JAM Trial Authors[36,37] (Japan)* 2016–2020	Symptomatic hemorrhage	100%	80 38:42 (84)	(B) D	0%	4 years	Vascular events, morbidity, mortality, and need for surgery.	Possible surgical advantage in patients with posterior hemorrhages or hemodynamic failure.	Retrospective non-prespecified subgroup analyses with various methodological limitations.

(B), bilateral; C, combined; Con-Med, number of patients in the conservative-medical group; D, direct; I, indirect; JAM, Japan Adult Moyamoya (Trial); MMD, moyamoya disease; MMS, moyamoya syndrome; NA, not available; Sur(Hemi), number of patients (hemispheres) in the surgical group.
* Refers to the JAM Trial.
Values in (parentheses) indicate the number of hemispheres or rate per operated hemisphere.

patients.[40] Postoperative vascular (ischemia or hemorrhage) complication rates on a per patient and per hemisphere basis for adult and pediatric patients were 12.9% and 7.9%, and 2.3% and 1.7%, respectively.

Possibly reflective of the increased surgical complication rate among adult patients was earlier data from a Japanese national registry that queried enrolled MMD patients regarding functional independence, and which raised a question as to the clinical benefit of surgery among adults. In 1997, the Japanese Research Committee on MMD conducted a national survey of 821 cases, and revealed no difference in reported clinical outcome between medically and surgically treated adult and pediatric patients.[41] A similar subsequent survey among patients <18 years old reported an advantage to surgical treatment,[42] raising the possibility that adult patients may have gained little or no benefit from surgical intervention.

Medical/surgical case–control series

A 2012 report from Saint Mary's Catholic University in Seoul, Korea, presented a retrospective analysis of 142 symptomatic adult patients presenting with ischemic or hemorrhagic events, 124 of whom were treated surgically (55% indirect, 22% direct, 23% combined) with 23 having bilateral procedures, and 18 of whom were treated medically (including 8 not considered for surgery due to debilitated neurologic status).[24] Demographic and angiographic severity grades were well matched but no data was provided on vascular risk factor profiles for the two groups. Mean follow-up period was between 4 and 5 years. Fewer vascular events (ischemic or hemorrhagic) were observed from surgery than with medical treatment in patients with ischemic presentation (19.1% *versus* 66.7%) and among those with a hemorrhagic presentation (17.1% *versus* 44.4%).* Survival curves, however, demonstrated a statistically meaningful advantage for surgery only in ischemic patients (log-rank $p < 0.05$) but not in the hemorrhagic group (log-rank $p > 0.05$). No postoperative complications were reported. Marked imbalances in the number of patients between the treatment groups, and lack of information on vascular comorbidities, limited any definitive conclusions from this analysis.

Also in 2012, the Academy of Military Medical Science in Beijing, China, provided a retrospective analysis of 802 patients, including 61.6% adults.[25] Of these patients, 773 patients were treated surgically (91% direct bypass), with 502 having bilateral surgeries for a total of 1274 procedures. Only 29 patients were treated conservatively, only 26 of whom survived initial hospitalization. Investigators were unable to contact 56 patients, and there was no comparison of demographic or clinical data between the treatment groups. Overall, postoperative vascular (ischemic or hemorrhagic) complications occurred in 5.8% of patients, with a 0% surgical mortality rate. Median follow-up period was 26 months. Among operated patients >18 years old, there was a cerebrovascular event rate of 13% at 2 years and 16% at 5 years, with a mortality rate of 1.8%. Among conservatively treated patients, there were no mortalities, hemorrhages, or infarctions, yielding a morbidity/mortality rate of 0% at 5 years. Substantial loss of data, marked imbalances in numbers between treatment groups, and omission of demographic and clinical data limit drawing any conclusions from this investigation.

In 2013, the Tiantan Hospital of Beijing, China, reported a retrospective analysis of 97 patients whose initial presentation was hemorrhagic, 93.8% of whom were adults.[26] Of the total patient population, 54 underwent revascularization surgery (54% direct, 20% combined, 7% indirect, 15% multiple craniostomies, and 4% carotid denudations) and 43 were treated conservatively. Median patient follow-up time was 7.1 years. Rehemorrhage occurred in 7.4% of surgical and 37.1% of conservatively treated patients ($p = 0.001$), and there were relatively fewer mortalities among the surgical group (3.7% *versus* 9.3%, $p = 0.476$). Patients with ischemic initial presentations were excluded from the investigation, and no data was provided on cerebral ischemic outcomes.

In 2015, investigators from the Samsung Medical Center in Seoul, Korea, presented an analysis of 104 adult patients with ischemic presentation, 45 of whom were treated surgically (100% indirect,

*Note that for each of the ischemic and hemorrhagicpopulations, surgical group percentages of vascular outcomes on a per-patient basis were abstracted from data provided in Tables 2 and 3 by combining the cumulative number of patients with an outcome from the various operative techniques, and dividing by the total overall number of surgical patients.

28.9% bilateral) and 59 nonsurgically.[28] Patients with hemorrhagic presentation or with syndromic/secondary disease were excluded. Surgical patients had worse angiographic grades ($p=0.004$) and perfusion scores ($p=0.005$), and less antiplatelet use ($p=0.025$), than the comparator. Median follow-up was 29 months in the medical, and 55 months in the surgical, treatment groups. Postoperative infarcts occurred in 13.3% of cases. Total infarct rate for surgical and medical patients was 26.7% and 13.6%, respectively, despite an improvement in perfusion from surgery. No patients developed hemorrhagic events. Hypertension, diabetes, PCA stenosis and perfusion deficits emerged as predictors of infarction. Baseline imbalances and delayed protection from indirect revascularization may have contributed to the observed lack of benefit from revascularization surgery in this investigation.

A 2015 report from the Tiantan Hospital in Beijing, China, provided a retrospective analysis of 528 symptomatic patients, including 60.4% adults.[29] Among these, 332 patients presented with ischemia and 196 with hemorrhage: among adults, 51% presented with hemorrhage while among pediatric patients 14% presented with hemorrhage. Overall, 406 were treated surgically (45.8% with direct, 47.8% with indirect, and 6.4% with combined revascularization techniques) and 122 patients (23.1%) were treated conservatively. Hemorrhagic presentation occurred in 75.4% of conservatively treated and 25.6% of surgical patients. Surgical vascular (ischemic or hemorrhagic) complications occurred in 1.5% of operated patients, with no mortalities reported. Overall, only 331 patients had at least 1 year follow-up, with complete data available on only 69% of surgical patients and 49% of medical patients: median follow-up time was 39 months. Substantially greater mortality was observed among patients presenting with hemorrhage than among those presenting with ischemia (4.8% *versus* 0.4%). Subsequent hemorrhages were less common in surgical than in medical patients (2.95% *versus* 41.7%, $p<0.01$), and subsequent infarcts were numerically less common in surgical than medical patients: 18.8% *versus* 28.3% ($p=0.099$). Incomplete data, marked imbalances between treatment groups, and lack of pertinent information on vascular risk factors, limits any reliable conclusions to be drawn from this investigation.

That same year, the investigators from Tiantan Hospital in Beijing also reported a retrospective analysis on 154 patients (involving 144 adults) presenting with intracranial hemorrhage (including intracerebral, intraventricular, subarachnoid, or combination of hemorrhage types).[30] In this analysis, 126 patients were treated surgically while 28 were treated conservatively. Of surgical patients, 124 had revascularizations (48% direct, 27% indirect, 25% combined) and 2 were treated by aneurysm obliteration only. Mean follow-up time was 36 months. Perioperative vascular (ischemic or hemorrhagic) complications occurred in 7.3% of patients. Subsequent hemorrhages occurred in 12.1% of surgical patients *versus* 21.4% of medically treated patients, and infarctions in 5.7% of surgical patients *versus* 10.7% of medical patients. Mortality rates were 7.3% in the surgical group, and 10.3% in the medically treated patients. Overall, no statistical differences emerged between surgical and medical treatment groups.

A 2016 report from the National University Hospital of Seoul, Korea, provided a retrospective analysis of 441 adult MMD patients presenting with a cerebral ischemic event, and compared clinical outcomes between 301 surgically (296 combined direct/indirect and 5 direct procedures) and 140 conservatively treated patients.[31] Per institutional protocol, revascularization surgery was considered indicated for MMD patients with cerebral ischemia and hemodynamic compromise on SPECT plus acetazolamide. Mean follow-up duration was 45 months in surgical patients and 77 months in the conservative group. Perioperative morbidity from cerebral infarction or hemorrhage was 2.6%, with 0.3% mortality. In total, 21 (15%) of conservatively treated patients ultimately required revascularization (comparative data subsequently censored). Cerebrovascular events occurred in 6% of surgical patients (3% ischemic and 3% hemorrhagic) and in 12.9% of conservatively treated patients (7.9% ischemic and 5% hemorrhagic). Annual rates of cerebrovascular events were 1.6% (.8% ischemic and 0.8% hemorrhagic) in surgical patients and 1.9% (1.2% ischemic and 0.8% hemorrhagic) in the conservatively treated group. At 1 year and 5 years, no statistical differences were observed in the rates of cerebrovascular events, ischemic or hemorrhagic, between the two groups. However, at 10 years the rate of ischemic events was lower in the surgical group than the conservative group (3.9% *versus* 13.3%, $p=0.019$), whereas again no difference was noted for hemorrhagic events (5.6% *versus*

6.2%, $p=0.413$). Notable in this investigation is an imbalance in the severity of disease between groups, with lower-severity grade 2/3 cases comprising 52% of surgical but only 9% of medical patients. In addition, whereas 89% of surgical cases were grades 2/3/4, 87% of conservative cases were grades 4/5.

In 2017, a consortium of hospitals in Korea retrospectively analyzed data from 249 adult symptomatic MMD patients, comprising 153 presenting with ischemia and 96 with hemorrhage, and among whom 158 had revascularization surgery (34% bilateral; 46% direct, 48% indirect, 6% combined) and 91 were managed medically.[32] Per institutional protocol, transdural anastomoses to fewer than two lobes on cerebral angiography constituted inadequate collateral flow, and mandated revascularization surgery. Data on medically treated patients who subsequently underwent a revascularization procedure was censored from the point of surgery onward. Treatment groups were generally well matched for most vascular risk factors and angiographic severity grade, but more medically treated patients had hypertension (33% *versus* 21%, $p=0.035$) and had hemorrhagic presentations (51.7% *versus* 31%, $p=0.001$) compared with the surgical patients. Primary outcome was a vascular event within 6 years, and median follow-up time was 2.32 years. Postoperative vascular complications occurred in 18.5% of patients in the form of 16.5% infarcts and 2% hemorrhages (8% infarcts and 0.9% hemorrhages per operated hemisphere). Among patients who presented with hemorrhage, revascularization led to fewer subsequent hemorrhages (6.1% *versus* 14.9%) and infarctions (4.1% *versus* 21.3%), whereas for those presenting with ischemia revascularization led to numerically fewer hemorrhages (1.8% *versus* 6.8%) but a greater number of recurrent ischemic events (17.4% *versus* 6.8%). Among medically treated patients presenting with hemorrhage, substantially more subsequent cerebrovascular events occurred than in those presenting with ischemia (40.2% *versus* 13.6%). In univariate log rank and multivariate regression analyses, surgery was beneficial in preventing any cerebrovascular event in hemorrhagic patients ($p<0.001$ for analyses) and among all patients overall ($p=0.004$ and $p=0.014$), but not in patients presenting with ischemic events ($p=0.887$, $p=\text{NA}$). Multivariate analyses also identified tobacco as the most consistent predictor of recurrent vascular events among all patients and subgroups. Despite an advantage in preventing recurrent events, no mortality benefit was observed for surgery in all patients ($p=0.279$) or in those with hemorrhagic presentation ($p=0.716$). Imbalances between the two groups, with more hypertension and hemorrhagic presentations among medically treated patients, may have biased the findings in favor of revascularization surgery.

A 2017 consortium of hospitals from Beijing, China, presented an interesting retrospective analysis of 82 MMD patients (164 hemispheres) with advanced disease, grades 4 ($n=113$), 5 ($n=45$), and 6 ($n=6$), 57% of which presented with hemorrhage and 43% with an ischemic event.[33] The investigation involved 89 surgical (100% direct technique) and 75 nonsurgical hemispheres. Clinical profiles and vascular risk factors were well matched between the two hemisphere groups. Vascular postoperative complications, all ischemic, occurred in 6.7% of surgical hemispheres. After a mean follow-up period of 55.1 months, 10.1% of surgically treated hemispheres and 9.3% of medically treated hemispheres experienced a new cerebrovascular event, despite substantial improvements in cerebral perfusion among the surgically treated participants ($p=0.003$). No differences were seen in functional status or mortality.

Later that year, the same investigators presented an analysis on 87 MMD patients aged ⩾50 years, 67% of whom presented with cerebral ischemia and 33% presented with cerebral hemorrhage.[34] Surgical revascularization was performed in 74 patients (bilaterally in 13 patients) for a total of 87 revascularized hemispheres (70% direct, 23% indirect, and 7% craniostomies only). Treatment groups were generally well balanced in terms of demographics and risk factor profile. The overall mean follow-up time was 35.5 months. Postoperative vascular complications occurred in 8.1% of patients (6.9% of hemispheres). Subsequent vascular events occurred in 12.2% of surgical patients and in 23.1% of conservative patients, resulting in no statistical difference between the two treatment groups.

In 2018, investigators from Johns Hopkins University presented a retrospective analysis of 94 adult and pediatric patients (184 hemispheres) with idiopathic or syndromic bilateral MMD managed conservatively (94 hemispheres) or by indirect revascularization (90 hemispheres).[35] A total of 74% of hemispheres were symptomatic, with 39%

infarcts, 29.3% transient ischemic attacks (TIAs), 6.04% hemorrhages, and 0.55% with both infarct and hemorrhage. Practice standards entailed conservative treatment for patients with no/minor symptoms, and those naïve to antiplatelet therapy or declining surgery. For patients with symptoms affecting daily function and activities, surgery was advised. The primary outcome measure was annualized ipsilateral cerebrovascular event rate, and mean duration of patient observation was 6.37 years. Postoperative complications included "infarcts", the numerical details of which were not provided. Overall annualized per-hemisphere risk of an ipsilateral vascular event was 0.93% for the surgical group and 2.7% for the conservative group. However, no differences were observed in vascular event-free survival (log rank $p=0.18$). For pediatric patients, annual per-hemisphere risk was 0% and 1.35% for the two treatment groups, whereas for adult patients annualized per-hemisphere risk was 2.86% and 2.18%, respectively.

Randomized controlled trial

In 2014, Miyamoto *et al.* published the results of the only prospective randomized trial on MMD, the Japanese MMD trial (JAM),[27] which enrolled 80 adult patients who experienced hemorrhage within 1 year, and allocated patients to bilateral direct STA-MCA revascularization ($n=42$) with or without additional indirect revascularization *versus* conservative therapy alone ($n=38$). The mean duration of observation was 4.32 years. No postoperative vascular (infarction or hemorrhage) or mortality complications occurred. Surgical patients experienced substantially fewer recurrent hemorrhages (11.9% *versus* 31.6%, $p=0.052$), but numerically more infarctions (2.4% *versus* 0%, $p=$ns) than the medically treated group. Outcome adjudication was not masked, and low enrollment prevented achieving the initial target goal of 160 patients, limiting statistical power. One particular criticism of this study was in regards to the 0% complication rate among 84 operated hemispheres which was in stark contrast to those reported in analogous non-MMD trials: 15% in the Carotid Occlusion Stroke Study (COSS)[43] and 12% in the External Carotid Internal Carotid (EC-IC) Bypass Study,[44] and raised concerns about the reliability of the report.[22,45]

Later subgroup analyses from JAM explored associations between hemorrhage occurrence and various angiographic/radiographic variables. Analyses identified an association between initial hemorrhage and choroidal artery anastomoses,[46] thalamic region collaterals[47] and PCA stenosis.[48] Analyses also identified choroidal anastomoses and PCA stenosis as determinants of posterior hemorrhages (thalamic, posterior temporal, parietal, occipital, posterior ventricle, or posterior callosum),[49] which predicted rehemorrhage.[36] Of these variables, posterior hemorrhage emerged as an indicator of surgical benefit, whereas surgery was ineffective for anterior hemorrhages.[36] Most recently, risk of rehemorrhage was linked to hemispheric hemodynamic failure (defined as impaired baseline perfusion or deficient perfusion reactivity to acetazolamide on SPECT), which in turn was related to PCA involvement.[37] In this analysis, revascularization was advantageous for those with hemodynamic failure but not in those with normal baseline and reactivity testing.[37] Innate constraints exist in the interpretation of data from retrospective non-prespecified subgroup analyses on such small numbers of patients. Additional limitations include the non-quantitative technique used to measure hemodynamic function, lack of data on patients with normal baseline perfusion but impaired reactivity, and absence of data regarding any ischemic outcome events. As the authors state, prospective investigations are needed to confirm subgroup analyses findings.

Meta-analyses

A 2018 meta-analysis attempted to elucidate whether surgery was beneficial in preventing symptomatic cerebrovascular events among (a) patients with symptomatic hemorrhage, (b) patients with symptomatic ischemia, or (c) those with any vascular symptoms, when compared with nonsurgical conservative/medical treatment.[50] Studies considered were those with quality scores of >5 which assessed patients >16 years old. Six studies were included, five retrospective and one randomized controlled trial: 3 studies of 204 patients in the hemorrhage group (65 medical *versus* 139 surgical), 2 studies of 553 patients in the ischemic group (149 medical *versus* 404 surgical), and 6 studies of 873 patients in the overall group (287 medical *versus* 586 surgical). Revascularization proved superior to medical management in the overall group [hazard ratio (HR) 0.301 (95% confidence interval (CI) 0.196–0.462) $p<0.0001$], hemorrhagic group [HR 0.319 (95% CI 0.150–0.678) $p=0.003$], and ischemic group [HR 0.240 (95% CI 0.059–0.987)

$p=0.048$]. No information was provided regarding specific outcomes of cerebral infarction or hemorrhage independently for the three groups, and mortality outcomes were not considered in the analysis.

A 2019 meta-analysis compared conservative/medical management with surgery in the prevention of recurrent cerebrovascular events.[51] Main inclusion criteria included trial quality scores of >5, and minimum duration of study subject observation of at least 6 months. A total of 5 studies consisting of 256 hemorrhagic patients, and 3 studies comprising 692 ischemic patients, were included for comparison between surgery and conservative treatment. Revascularization proved superior to medical management in the overall population [HR 0.404 (95% CI 0.279–0.585) $p<0.001$] yet did not change mortality [HR 0.372 (95% CI 0.120–1.154) $p=0.087$]. Revascularization was also superior in patients presenting with hemorrhage [HR 0.259 (95% CI 0.138–0.486) $p<0.001$], but not in those presenting with ischemia [HR 0.470 (95% CI 0.140–1.579) $p=0.222$]. No data was provided regarding type of cerebrovascular outcomes in treatment groups.

The 2019 meta-analysis by Wouters *et al.* provided specific information pertaining not only to clinical presentation group (hemorrhagic or ischemic), but also to specific vascular outcome types (hemorrhage and infarction) as well as mortality.[52] When limiting analyses to adult patients, 5 studies provided 999 patients presenting with hemorrhage or infarction, 4 studies provided 374 hemorrhage patients, and 3 studies provided 694 infarct patients. In the overall population [OR 0.48 (95% CI 0.31–0.75)] and in the hemorrhagic group [OR 0.36 (95% CI 0.19–0.68)], surgery was superior to conservative treatment for preventing a recurrent event. However, no advantage to revascularization surgery was observed among patients presenting with an ischemic event [OR 0.54 (95% CI 0.14–2.03)]. Similarly, surgery proved advantageous in preventing future hemorrhage [OR 0.27 (95% CI 0.14–0.53)] but did not prove beneficial in preventing future infarction [OR 0.71 (95% CI 0.46–1.09)]. A reduction in mortality from surgery was also observed [OR 0.32 (95% CI 0.13–0.77)].

The objective of another 2019 meta-analysis was to compare conservative treatment with surgery, and secondarily to compare surgical modalities.[53] All studies had ranked quality scores of >5. The analysis included 20 studies, all of which were retrospective analyses except for one prospective randomized trial, and involved a total of 2287 patients with 1525 surgical and 762 medical cases. Surgery was advantageous in preventing subsequent vascular events in the overall group [OR 0.26 (95% CI 0.2–0.33) $p<0.001$] and in the hemorrhagic patients [OR 0.21 (95% CI 0.14–0.33) $p<0.001$], but not in patients presenting with an ischemic event [OR 0.58 (95% CI 0.16–2.05) $p=0.396$]. Specific details regarding the vascular outcome types were not presented.

Discussion

Obvious limitations exist in interpreting, and drawing conclusions from, the recent investigations. The retrospective nature of most studies, the frequent loss of data points, marked imbalances in patient numbers and characteristics between treatment groups, lack of consistently defined medical treatments, absence of standardization in surgical technique, and lack of adequate statistical methodology are simply a few. Nevertheless, and contrary to prevailing views that surgery is a uniformly indicated treatment for MMD, the variable, inconsistent, and at times conflicting findings of these investigations raise serious questions about the perceived advantages of surgery among certain subgroups of patients and for various clinical outcomes. The large proportions of conservatively treated patients among the various investigations, and most notably in the study on advanced disease,[33] underline the true uncertainty that exists regarding optimal treatment for MMD patients.

From the reviewed literature, several salient observations emerge, including the possibility that revascularization may be less beneficial in patients presenting with ischemic symptoms compared to those presenting with hemorrha ges,[28,32,51–53] that surgery may be less effective in preventing subsequent ischemic events than hemorrhagic ones,[27,29,30,32,52] and that surgery may entail greater risk of adverse complications and be less advantageous in adults than in pediatrics.[35,36,38–40] These findings are especially relevant when considering that, for patients in the United States and Europe, MMD commonly presents in adults, and typically manifests as, and remains predominantly, an ischemic cerebrovascular disease.[13] As such, surgery may play a more limited role in the management of non-Asian patients. An additional important question that arises is whether data from East Asia, where MMD is more of a pediatric disease and is mostly hemorrhagic in presentation,[15] can be at all extrapolated to non-Asian populations.

Some authorities have suggested that asymptomatic and minimally symptomatic MMD may represent an adapted or compensated physiologic state maintained by an extensively developed network of protective collateral vessels,[18] and that microvascular flow patterns may potentially become disrupted and compromised by revascularization surgery.[54] Analogously, perioperative infarctions in the COSS trial have been attributed to complex hemodynamic alterations within the existing anastomotic system, and not to thrombotic occlusion or technical failure of the nascent anastomotic connection created.[55] From the available datasets reviewed, postoperative cerebrovascular complication rates varied considerably, ranging from 2% to 18%, underscoring the fact that surgery is not without risk, and the importance of informed decision making regarding patient selection.

Alternatively, nonsurgical treatment is frequently termed ‘conservative’ or ‘medical’ and is rarely adequately defined or documented. Usually no mention is made of specific medications, of attempts towards risk factor modification, of efforts to ensure adequate consistent hydration, or of strategies to augment systemic pressures so as to prevent hypoperfusion and ischemia. As such, no standardization in medical therapy exists against which to compare surgical treatment, despite evidence for traditional risk factors being predictors of recurrent vascular events,[18,28,32] official guidelines recommending the use of antiplatelet agents,[1] data that vasodilators may improve perfusion in symptomatic ischemic hemispheres,[56] and evidence linking an MMD genetic susceptibility variant to the development of anterior circulation large artery atherosclerosis, in which case HMG Co-A reductase inhibitors may theoretically prove useful.[57] The frequent presence of sonographically detected microemboli also reinforces the potential importance of antiplatelet agents in preventing thromboembolic infarctions in MMD.[16,58] Of concern may be the possibility that ‘conservative’ treatment often implies no active medical treatment. In the absence of concrete clinical evidence with which to direct management of patients with MMD, diagnostic imaging modalities (angiography, cerebral MRI, perfusion scans) are frequently employed to assist in prognostication, and to potentially direct therapeutic decisions.[59] Grading systems that score diagnostic modalities based on disease severity have been formulated to predict which patients are most likely to become symptomatic, and thus possibly identify those that may most benefit from revasscularization.[59–62] Unfortunately, many of the principal diagnostic modalities employed are of limited precision, as patients with advanced angiographic disease may be asymptomatic,[18] and patients with severely compromised cerebral perfusion may be no more likely to become symptomatic than those with normal perfusion.[18,33,59,63]

Conclusion

The inadequacy of available clinical investigations, frequently with conflicting and contradictory findings, underlines the pressing need for adequate clinical trials to define which patient groups may benefit from surgery, and which ones may require only medical therapy. Identification of subgroups that may or may not require surgery based on clinical and radiological parameters will be paramount, including the presence or absence of symptomatology, ischemic or hemorrhagic presentation, angiographic stage of disease, and severity of perfusion defect. Standardization of medical therapies and surgical techniques among participating institutions, and comparison of direct and indirect revascularization methods, will provide crucial information pertinent to patient management. Lingering questions will only be answered by randomized, controlled trials which will preferably be multinational so as to elucidate the role of surgery among various populations.

Several active Chinese trials may provide crucial information towards answering these questions. The Effect of Surgical Revascularization on Hemorrhagic Moyamoya Disease (ESRHMMD) trial will randomize 108 adult hemorrhagic MMD patients to one of three treatment strategies: conservative management, direct revascularization, or indirect revascularization.[64] The similar but larger Adult Hemorrhagic Moyamoya Surgery Study (AHMMS) will aim to randomize 360 adult hemorrhagic MMD patients to conservative treatment *versus* direct revascularization.[65] The ongoing

Carotid and Middle cerebral artery Occlusion Surgery Study (CMOSS) will randomize 330 adult patients with ischemic symptoms from ICA or MCA occlusion plus hemodynamic failure to direct EC-IC surgery *versus* optimal medical management which will entail antiplatelet therapy and vascular risk factor modification.[66] While not specifically focusing on MMD, CMOSS may provide valuable analogous information for the treatment of patients with intracranial occlusions and hemodynamic compromise.

Despite these important contributions, similar American and European trials will also be needed. It has recently been estimated that over 20,000 patients have been enrolled in the various major carotid endarterectomy and stenting trials.[67] In these trials, objective clinical equipoise superseded preexisting treatment beliefs (and biases), and quieted concerns that such investigations were unethical and denied patients optimal (surgical) treatment. A similar philosophy may be required for patients with MMD.

The main limitation of this work is that it is a perspective or general review of the literature and did not employ the standardized methodology of a formal systematic review or meta-analysis. However, every attempt and effort was made to be as complete as possible in searching the literature and acquiring the pertinent articles, and the conclusions of this work are concordant with those of the most recent meta-analyses.

Conflict of interest statement

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