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EDITORIAL

Is medical management useful in Moyamoya disease?

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Abstract

Moyamoya disease (MMD), characterized by progressive internal carotid artery stenosis and collateral vessel formation, prompts cerebral perfusion complications and is stratified into idiopathic and Moyamoya syndrome subtypes. A multifaceted approach toward MMD management addresses cerebral infarctions through revascularization surgery and adjunctive medical therapy, while also navigating risks such as intracranial hemorrhage and cerebral infarction resulting from arterial stenosis and fragile collateral vessels. Addressing antithrombotic management reveals a potential role for treatments like antiplatelet agents and anticoagulants, despite the ambiguous contribution of thrombosis to MMD-related infarctions and the critical balance between preventing ischemic events and averting hemorrhagic complications. Transcranial doppler has proven useful in thromboembolic detection, despite persisting challenges concerning the efficacy and safety of antithrombotic treatments. Furthermore, antihypertensive interventions aim to manage blood pressure meticulously, especially during intracerebral hemorrhage, with recommendations and protocols varying based on the patient's hypertension status. Additionally, lipid-lowering therapeutic strategies, particularly employing statins, are appraised for their possible beneficial role in MMD management, even as comprehensive data from disease-specific clinical trials remains elusive. Comprehensive guidelines and protocols to navigate the multifaceted therapeutic avenues for MMD, while maintaining a delicate balance between efficacy and safety, warrant further meticulous research and development. This protocol manuscript seeks to elucidate the various aspects and challenges imbued in managing and navigating through the complex landscape of MMD treatment.

Key Words: Moyamoya disease; Cerebral infarction; Antithrombotic management; Transcranial doppler; Revascularization; Intracerebral hemorrhage; Antihypertensive intervention; Lipid-lowering therapies

Core Tip: Moyamoya disease (MMD) involves progressive arterial stenosis, leading to cerebral infarctions and hemorrhages. Key treatments include revascularization surgery and supplementary medical therapy. Antithrombotic management, crucial for ischemic stroke prevention in MMD, requires a careful balance due to bleeding risks. Understanding cerebral infarction pathways, involving hemodynamic impairment and thromboembolism, is essential. Transcranial doppler is useful for emboli detection and screening. Antiplatelet therapy, especially Acetylsalicylic acid, is common, but its efficacy varies. Antihypertensive management is recommended during initial hemorrhage phases, while lipid-lowering strategies like statins show potential but need more research for specific guidelines in MMD.

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INTRODUCTION

Moyamoya disease (MMD) is delineated by progressive stenosis of the internal carotid arteries intracranially, consequentially instigating impeded cerebral perfusion. This chronic cerebrovascular disorder encompasses the gradual occlusion of both distal internal carotid arteries, which is somewhat mitigated by the proliferation of collateral vessels at the brain's base. Cerebral infarction may manifest due to reduced blood flow incited by arterial stenosis and occlusion. Furthermore, the fragility of compensatory collateral vessels poses a risk of rupture, thereby precipitating intracranial hemorrhage[1]. MMD is categorized into two subtypes: idiopathic (primary) and Moyamoya syndrome (secondary)[2]. The pathogenesis of the primary form is largely idiopathic, albeit associations with the RFN213 (ring finger protein 213) on chromosome 17q25.3 have been posited[3]. Contrarily, Moyamoya syndrome, while sharing angiographic characteristics with the primary subtype, is concurrently associated with additional pathologies, including but not limited to head and neck radiation, atherosclerosis, and systemic lupus erythematosus[4]. Key angiographic indicators of MMD encompass: (1) stenosis or occlusion of the distal internal carotid artery or the anterior/middle cerebral artery's proximal segment; (2) a smoky appearance in collateral vessels distal to the associated stenosis; and (3) bilateral involvement[5].

The incremental arterial constriction within the Circle of Willis in MMD ultimately progresses to total occlusion, thus diminishing blood flow and culminating in potential cerebral infarction[6]. A longitudinal study executed in Japan (2007) revealed a 3.2% annual stroke rate amongst 34 primary MMD patients without surgical intervention, with a mean follow-up duration of 44 mo[7,8]. Addressing the attenuated blood flow through revascularization surgery is the primary modality for cerebral infarction management, rendering surgical intervention indispensable, whereas medical therapy functions as an adjunct treatment in MMD scenarios[9].

"Moyamoya", linguistically derived from Japanese, metaphorically describes the "puff-of-smoke" visual evident in angiography, corresponding to the collateral vessels formed subsequent to stenosis. These fragile collateral vessels, while compensatory, introduce a pronounced susceptibility to rupture and intracerebral hemorrhage. Notably, revascularization techniques can alleviate the stresses on these collaterals, thus mitigating rupture risk[10]. Contrastingly, spontaneous intracerebral hemorrhage predominantly originates from microaneurysm rupture, frequently corollary to chronic hypertension[11]. The meticulous management of blood pressure is imperative in spontaneous intracerebral hemorrhage cases[12,13], with antihypertensive medications occupying a pivotal role in therapeutic strategies[13]. Nonetheless, the efficacy of blood pressure reduction *via* antihypertensive medications remains to be elucidated in the context of intracerebral hemorrhage among MMD patients.

ANTITHROMBOTIC MANAGEMENT IN MMD

Antithrombotic interventions in ischemic stroke fundamentally aim at hindering the development of blood clots[14]. A spectrum of such treatments incorporates antiplatelet agents, anticoagulants, and thrombolytic drugs. In the context of MMD, where hemodynamic impairment is pivotal in brain ischemia[15], there emerges an ambiguity regarding the degree to which thrombosis contributes to infarction events within this disease profile. Despite this, the potential for thromboembolism with ensuing clot formation in infarction events in MMD necessitates consideration[16], rendering the role of antithrombotic treatments potentially significant in preemptively addressing infarctions[17].

Elucidation of cerebral infarction pathways

Various research delineates that cerebral infarction in MMD is not exclusively the consequence of hemodynamic impairment. Larson *et al*[18] elucidated a propensity of Moyamoya patients towards a pro-thrombotic state. While Shulman *et al*[19] exhibited evidence of emboli connected to stenotic arteries in distinct Moyamoya cases. Furthermore,

Jeon *et al*[20] identified that emboli, detected as high-intensity transient signals and distal to high-grade stenotic arteries, were etiological in recent cerebral infarctions. These revelations underscore that both hemodynamic impairment and thromboembolism are instrumental in cerebral infarction within MMD[21].

Transcranial doppler in thromboembolic detection

Transcranial doppler (TCD) has proven to be a dependable point-of-care tool for detecting emboli[22]. Several studies amplify the significance of TCD in unveiling thromboembolic occurrences in MMD. Since the 1980s, TCD has been entrenched as a methodological approach for screening individuals with sickle cell disease and Moyamoya syndrome, particularly regarding the necessity for blood transfusions as a primary stroke preventative strategy[23]. It has also been propounded that TCD could be potentially efficacious for screening asymptomatic Moyamoya patients to discern the necessity for antiplatelet treatment as a preemptive measure against stroke.

Challenges in antithrombotic treatment efficacy

Although devoid of robust evidence from randomized controlled trials (RCTs), the administration of antiplatelet treatment persists among physicians treating Moyamoya patients with cerebral infarction or transient ischemic attacks (TIAs)[24,25]. The prevalent pharmacologic inclination predominantly resides with a single antiplatelet treatment utilizing Acetylsalicylic acid (ASA). Contrastingly, primary stroke prevention employing antithrombotic treatment often goes unacknowledged for asymptomatic Moyamoya patients[24]. A retrospective study did not validate the utilization of antiplatelet therapy as a predominant prophylactic measure for ischemic events in MMD under conditions of stable hemodynamic status[26].

In managing MMD, surgical intervention is the predominant therapeutic strategy. Notwithstanding, surgeons frequently elect to administer antiplatelet pharmaceuticals subsequent to revascularization procedures[24,27-30]. The deployment of antithrombotic treatment post-surgical revascularization is quintessential, engendering improvements in circulation, the preservation of cerebral perfusion, thrombus prevention, and the maintenance of hemodynamic stability through the bypass system[24,29-31]. ASA remains the preferred post-operative antiplatelet agent among surgeons[30, 32]. In an investigation by Onozuka *et al*[33], approximately 2000 Japanese patients, hospitalized due to non-hemorrhagic events associated with MMD, demonstrated improved functional outcomes when pre-admitted antiplatelet medication was administered.

Alternative antiplatelet agents, namely Clopidogrel and Cilostazol, have demonstrated propitious outcomes in averting ischemic stroke among individuals diagnosed with MMD[24]. Cilostazol, frequently prescribed in Japan and Korea, is utilized to shield against ischemic stroke in patients with MMD[24,34], while ASA and Clopidogrel are more prevalent recommendations outside these regions[35]. According to a study by Seo *et al*[34], a cohort of nearly 10000 Korean Moyamoya patients showcased augmented survival rates when administered any antiplatelet drug, with a particular inclination toward Cilostazol. Additionally, research by Kim *et al*[36] implies that Cilostazol may decelerate the progression of intracranial vessel constriction in Moyamoya patients. Notably, the application of Cilostazol seems to amplify cerebral blood flow and cognitive functionality in Moyamoya patients more substantially than Clopidogrel[37, 38]. However, a study by Yamada *et al*[29] did not identify tangible benefits of any antiplatelet therapy in precluding recurrent ischemic stroke among 344 Moyamoya patients with a history of TIA or preceding infarct events in Japan.

In the context of MMD, evidence supporting the utilization of a dual antiplatelet regimen is absent. Given the amplified risk of intracranial hemorrhage, such a regimen might be unsuitable for patients with MMD, even in scenarios where a single regimen proves ineffectual. Nonetheless, there have been documented instances wherein a dual antiplatelet regimen was implemented for patients who either refused revascularization surgery or were awaiting the procedure[39,40]. The most recent Japanese management guidelines for MMD advocate for the employment of antiplatelet therapy as a secondary preventive measure against cerebral infarction, albeit with a grade C recommendation level, signifying a potential consideration in the absence of substantial scientific justification[41,42]. The protracted utilization of antiplatelet therapy for the secondary prevention of ischemic events continues to be a subject of debate due to the elevated risk of intracranial hemorrhage[25,41,43].

Navigating through anticoagulants and thrombolysis

Delving into the anticoagulant spectrum, which consists of warfarin, unfractionated heparin, low-molecular-weight heparin, and direct oral anticoagulants, these potent antithrombotic agents present a conspicuous risk of inducing bleeding complications. Hence, in MMD, which intrinsically carries a heightened risk of intracerebral hemorrhage, the employment of anticoagulants to preempt ischemic stroke is generally contraindicated[44,45], albeit with exceptions noted in scenarios where MMD coexists with conditions endorsing a hypercoagulable state[46-48]. Concerning thrombolysis, while intravenous recombinant tissue plasminogen activator (rt-PA) is conventionally utilized in acute ischemic stroke[49], its application within the thromboembolic mechanisms of MMD raises concerns due to the significantly elevated incidence of associated intracranial bleeding[50] and warrants cautious contemplation[41,42].

For Moyamoya patients confronting cerebral infarction or TIA, and seeking secondary stroke prevention, a single antiplatelet regimen comprising ASA, Clopidogrel, or Cilostazol may be proposed. Additionally, selective Moyamoya patients demonstrating embolic detection *via* TCD monitoring might benefit from antiplatelet treatment for primary ischemic stroke prevention. Nevertheless, the prudent utilization of certain anticoagulants and intravenous rt-PA, especially in Moyamoya patients enduring acute ischemic episodes, necessitates meticulous evaluation due to potential adverse impacts.

Table 1 provides a succinct overview of recommended antithrombotic treatment modalities in MMD, emphasizing a cautious approach in the management and treatment selection for these patients, given the delicate balance between

Table 1 The antithrombotic treatment for Moyamoya disease

Antithrombotic treatment	Rationale
Single antiplatelet regimen [agents: ASA (50-325 mg) per day; clopidogrel (75 mg) per day; cilostazol (200 mg) per day]	Primary stroke prevention in embolic detection by TCD; Secondary stroke prevention
Dual antiplatelet regimen	No role
Anticoagulant	Contra-indicated
Thrombolysis	Use with caution

ASA: Acetylsalicylic acid; TCD: Transcranial doppler.

preventing ischemic events and avoiding hemorrhagic complications.

ANTIHYPERTENSIVE INTERVENTION IN MMD

A meticulous scrutiny of the 2012 and 2021 Japanese MMD management guidelines postulates a recommendation to administer antihypertensive pharmacological agents during the incipient phase of intracerebral hemorrhage with the objective of mitigating hematoma expansion. However, a specificity pertaining to target blood pressure (BP) during this phase is conspicuously absent[41,42].

Antihypertensive recommendations during intracerebral hemorrhage

Within the confines of the aforementioned guidelines, a systolic BP < 180 mmHg and a diastolic BP < 105 mmHg are propounded for Moyamoya patients undergoing an intracerebral hemorrhage during the initial phase, substantiated by level III evidence[41]. Subsequent recommendations from the 2021 guidelines imply that attenuation of systolic BP during the acute stage of hemorrhagic events may be judicious, cognizant of the concomitant risk of cerebral ischemia. The recommendation is assigned a grade C, with a concomitant low level of evidence[42].

BP management and clinical outcomes

Extrapolating data from clinical outcomes of Moyamoya patients in China suggests a pronounced correlation between severe uncontrolled hypertension and unfavorable results, establishing severe uncontrolled BP as an independent risk factor[51]. An elevation in BP ostensibly exacerbates the risk of cerebrovascular events even in asymptomatic Moyamoya patients[52].

Antihypertensive protocols for moyamoya patients with hypertension

Employing antihypertensive treatment, particularly in Moyamoya patients manifesting hypertension, ostensibly aids in obviating unfavorable outcomes. For these patients, a protracted antihypertensive treatment is prudent, with targets conforming to hypertensive management guidelines. First-line antihypertensive agents, including Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Thiazide diuretics, and dihydropyridine Calcium-channel blockers, are reiterated by standard guidelines for hypertension management in this context[53].

Caution against prophylactic antihypertensive use

Conversely, a methodical administration of antihypertensive agents in Moyamoya patients without a definitive hypertension diagnosis is not advocated[41].

Table 2 provides a succinct overview of antihypertensive interventions and their respective rationale in the management of MMD.

LIPID-LOWERING THERAPEUTIC STRATEGIES IN MMD

The potential efficacy of lipid-lowering interventions in MMD invites further scrutiny, given the insufficiency of direct, disease-specific clinical trial data to substantiate this therapeutic approach. Within the context of lipid-lowering agents, statins emerge as a notably beneficial category, demonstrating prophylactic utility against both primary and secondary ischemic strokes in cohorts presenting with extant atherosclerotic disease[54,55]. Insight derived from Church *et al*[56] infers that statins, recognized for their pivotal role in atherosclerosis management, might also modulate the trajectory of unilateral MMD, thereby attenuating its progression. Moreover, following encephaloduroarteriosynangiosis surgery, atorvastatin has been implicated in fostering collateral blood vessel formation in patients with MMD[57]. Although Japanese guidelines advocate for lipid-lowering therapy in Moyamoya patients concomitant with dyslipidemia, a precise target lipid profile is requisite for such treatment modality yet awaits rigorous establishment[41]. Tentatively, aligning low-density lipoprotein levels below 100 mg/dL *via* statin administration could be considered a rational objective in

Table 2 Delineation of antihypertensive strategies in Moyamoya disease

Antihypertensive treatment	The rationale of treatment in Moyamoya disease
Nicardipine 5-15 mg/h; Labetalol 10 mg IV over 1-2 min followed by infusion of 2-8 mg/min	The early stage of intracerebral hemorrhage
Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Calcium channel blockers (highly lipophilic); Diuretics	Presenting concurrent hypertension: primary and secondary prevention for cerebral ischemia or hemorrhage

Moyamoya patients, mirroring recommendations applicable to alternate stroke patients with confirmed atherosclerotic disease.

Table 3 elucidates specific lipid-lowering agents and their respective rationales in managing MMD, thereby highlighting the complexities and considerations intrinsic to this therapeutic domain. Future research endeavors necessitate a focus on delineating the intricacies of lipid management in this pathological context, thereby paving the way for enhanced, evidence-based clinical practices and patient outcomes.

CONCLUSION

The primary treatment approach for MMD is surgical revascularization, while medical therapy is used as a supplementary treatment. Antithrombotic therapy, such as antiplatelet medications, anticoagulants, and thrombolytic drugs, may be employed to prevent infarctions in MMD. Although hemodynamic impairment is the primary cause of infarction, thromboembolism can also contribute. TCD monitoring can aid in detecting emboli and guide the use of antiplatelet treatment. Commonly used antiplatelet medications include ASA, clopidogrel, and cilostazol. However, the routine use of antithrombotic drugs in MMD lacks strong evidence from RCTs. Antihypertensive treatment is recommended for Moyamoya patients, particularly during the early phase of intracerebral hemorrhage, to prevent hematoma expansion. The target blood pressure remains uncertain, but it is suggested to maintain systolic blood pressure below 180 mmHg and diastolic blood pressure below 105 mmHg. Hypertension is a risk factor for poor outcomes in Moyamoya patients, and long-term antihypertensive treatment is advised for those with established hypertension. First-line antihypertensive agents include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, and calcium channel blockers. The effectiveness of lipid-lowering treatment in MMD is not well-established. However, statins have demonstrated benefits in preventing ischemic strokes in patients with atherosclerotic disease and may also slow the progression of MMD. Further research is necessary to determine the role of lipid-lowering therapy in MMD.

Table 3 Analyzing lipid-lowering therapeutic interventions in Moyamoya disease

Lipid-lowering agent	Corresponding rationale in Moyamoya disease treatment
Statins	Addressing concurrent dyslipidemia (LDL > 100)
	Facilitating collateral development post-EDAS
Fibrate	Literature provides no extant findings

LDL: Low-density lipoprotein; EDAS: Encephaloduroarteriosynangiosis.

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