Chapter

Medical Management in Moyamoya Disease

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Abstract

Medical treatment seems to be not entirely helpful in the treatment of Moyamoya disease. No evidence supports the benefits of any drug treatment in Moyamoya disease. The ischemic or hemorrhagic event in Moyamoya disease is not preventable with any medical treatment. However, most of the physicians still prescribe the antithrombotic drug for Moyamoya patients with an ischemic event. Moreover, the standard guidelines recommend administering antithrombotic medications to treat Moyamoya with the ischemic event, even the risk of hemorrhagic complication. Antihypertensive drugs are routinely prescribed in Moyamoya patients with or without elevated blood pressure. A literature review about medical treatment in Moyamoya disease should help determine its use in this pathologic condition.

Keywords: Moyamoya disease, antithrombotic drugs, antiplatelet therapy, antihypertensive drugs, lipid-lowering drugs

1. Introduction

Moyamoya disease is a chronic steno-occlusive cerebrovascular disease characterized by progressive occlusion of bilateral distal ICA with a fine basal collateral network development. Long-term hemodynamic stress through the basal collateral network leads to cerebral ischemia and intracranial hemorrhage in children and adults, respectively. The study from Japan in 2007 reported the annual risk of any stroke as 3.2% in 34 non-surgically treated Moyamoya patients (mean follow up over 44 months) [1, 2].

Progressive stenosis of distal intracranial internal carotid arteries with a smoke-like appearance from collateral vessels in angiography is characteristic of Moyamoya disease [3]. The stenosis usually remains progressive until occlusion and flow diminish. Hemodynamic collapse is a primary mechanism for an ischemic event in Moyamoya disease. The preferred treatment for cerebral ischemia focuses on the correction of hemodynamic failure. This rationale makes surgical treatment essential, and medical management is not a principle for Moyamoya patients [4].

The name of moyamoya means puff of smoke, which refers to the collateral circulation's angiographic appearance. These collaterals are bundles of small, fragile arterioles that vulnerable to break out. The rupture of weak collateral vessels in Moyamoya disease is a primary mechanism for a hemorrhagic event. Revascularization surgery can reduce overload in collateral vessels, which prevents

the vessels from getting ruptured [5]. In contrast, primary intracerebral hemorrhage is related to chronic hypertension [6]. The role of blood pressure control with antihypertensive drugs is not entirely clear for intracranial hemorrhage prevention in Moyamoya patients.

2. Methods

NU, SP, and SM independently search the Pubmed, MEDLINE, and Google Scholar for medical management in Moyamoya disease using the term "antithrombotic" or "antiplatelet" or "anticoagulant" or "thrombolytic" or "antihypertensive" or "lipid-lowering" or "aspirin" or "clopidogrel" or "cilostazol" or "warfarin" or "recombinant tissue plasminogen activator" and "Moyamoya."

2.1 The role of antithrombotic therapy in Moyamoya disease

Antithrombotic therapy consists of antiplatelet, anticoagulant, and thrombolytic agents. The rationale of antithrombotic is to prevent thrombogenesis [7]. It is not very confident that the ischemic event in Moyamoya disease is associated with thrombogenesis. The disease's pathogenesis lacks cerebral blood flow due to progressive stenosis of corresponding arteries rather than thrombo-embolism causes brain ischemia in Moyamoya patients. The role of antithrombotic therapy for ischemic prevention in Moyamoya disease is also not absolute.

However, hemodynamic failure may not be the only mechanism responsible for cerebral ischemia in Moyamoya disease. Larson et al. demonstrated that Moyamoya patients are predisposed to a pro-thrombotic state [8]. Shulman et al. reported evidence of artery-to-artery emboli in two separate Moyamoya cases. In the first patient, the emboli were visualized distally from the stenotic artery during bypass surgery. In the second case, the authors detected the emboli as a high-intensity transient signal (HITS) by transcranial Doppler (TCD) [9]. Jeon et al. reported the correlation between the emboli detected as HITS by TCD and the recent cerebral infarct [10]. The results of these two studies imply that hemodynamic compromise might not be the only mechanism for cerebral ischemia in Moyamoya patients. The evidence of artery-to-artery emboli opens up the role of antithrombotic therapy in Moyamoya disease. However, no clinical trial supports the use of antithrombotic drugs in Moyamoya disease.

Although there is no evidence to support clinical benefit, physicians still prescribe an antiplatelet agent as cerebral ischemic prevention in Moyamoya patients with symptomatic ischemic events or transient ischemic attacks (TIAs) [11, 12]. The single antiplatelet regimen with Aspirin is the most popular among the physicians. Most physicians prefer no antithrombotic treatment in asymptomatic Moyamoya patients [11]. Surgeons usually prescribe an antiplatelet agent after revascularization surgery [5, 11, 13–15]. After the surgery, antiplatelet treatment benefits include improving circulation to preserve cerebral perfusion, preventing small thrombus, and maintaining blood flow through surgical bypass [11, 14–16]. Aspirin remains the most popular antiplatelet agent prescribed by surgeons after surgery [15, 17]. Onozuka et al. reported that nearly 2,000 patients from Japan with non-hemorrhagic Moyamoya disease who received antiplatelet therapy before admission had better functional status than those who did not [18].

Other antiplatelet agents, such as Clopidogrel and Cilostazol, are also useful for ischemic prevention in Moyamoya disease [11]. Japanese and Korean physicians have the most experienced using Cilostazol in Moyamoya patients [19, 20]. Seo et al.'s upcoming report showed that nearly 10,000 patients from Korea who were

prescribed antiplatelet benefited from reducing mortality, especially patients who received Cilostazol [21]. In contrast, Yamada et al. showed no benefit of antiplatelet treatment to prevent recurrent cerebral infarction in 344 Moyamoya patients with TIA or previous ischemic events in Japan [14].

The dual antiplatelet regimen has no role in Moyamoya disease, even in single regimen failure, due to the high risk for bleeding complications. The Japanese guidelines for Moyamoya disease management recommend using antiplatelet therapy as cerebral ischemic prevention, but with grade C level (can be considered, but adequate scientific rationale lacking) [22]. The long-term use of antiplatelet therapy for secondary ischemic prevention remains controversial because of the high risk for intracranial hemorrhage [12, 22].

The anticoagulants consist of the vitamin-K antagonist, heparin, low-molecular-weight heparin (LMWH), and non-vitamin-K antagonist. Due to the high risk of bleeding in Moyamoya disease, anticoagulants have no role in ischemic prevention, even in surgical or antiplatelet failure. Intravenous thrombolytic treatment with the recombinant tissue plasminogen activator (rtPA) is a standard treatment in acute ischemic stroke [23]. The Japanese guidelines for Moyamoya disease management recommend not giving the rtPA during acute ischemic stroke presentation due to the high risk of bleeding [22].

In summary, the single antiplatelet regimen with Aspirin, Clopidogrel, or Cilostazol may be useful for secondary ischemic prevention in Moyamoya patients with cerebral infarct or transient ischemic attack (TIA). The anticoagulants with the vitamin-K antagonist, heparin, low-molecular-weight heparin (LMWH), or non-vitamin-K antagonist have no role in Moyamoya patients. Intravenous rtPA has no role in Moyamoya patients with acute ischemic stroke. **Table 1** shows a summary of antithrombotic therapy in Moyamoya disease.

2.2 The role of antihypertensive treatment in Moyamoya disease

The Japanese guidelines for Moyamoya disease management recommend giving antihypertensive drugs to control blood pressure during the acute phase of intracranial hemorrhage for preventing hematoma expansion. However, the target blood pressure during the acute phase of intracranial hemorrhage is unclear. During the acute phase of intracranial hemorrhage in Moyamoya patients, the guidelines postulate that systolic and diastolic blood pressure should be under control below 180 and 105 mmHg, respectively, without any clinical evidence.

Comparing clinical outcomes between Moyamoya patients with and without hypertension in China shows that severe untreated hypertension is an independent risk factor for unfavorable outcomes [24]. Antihypertensive drugs could prevent patients with hypertension from unfavorable outcomes. Long term antihypertensive treatment is only for Moyamoya patients with hypertension. The target blood

Antithrombotic treatment	The role of treatment in Moyamoya disease
Antiplatelet	Secondary prevention for cerebral ischemia Agents: Aspirin (50–325 mg) Clopidogrel (75 mg) Cilostazol (200 mg)
Anticoagulant	No role
Thrombolysis	No role

Table 1.
The role of antithrombotic treatment in Moyamoya disease.

Antihypertensive treatment	The role of treatment in Moyamoya disease
• Nicardipine 5–15 mg/hour • Labetalol 10 mg IV over 1–2 minutes followed by infusion of 2–8 mg/min	The acute phase of intracranial hemorrhage
• Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Calcium channel blockers (highly lipophilic) • Diuretics	Presenting concurrent hypertension: secondary prevention for cerebral ischemia or hemorrhage

Table 2.
The role of antihypertensive treatment in Moyamoya disease.

Lipid-lowering therapy	The role of treatment in Moyamoya disease
• Statins	Presenting concurrent dyslipidemia (LDL > 100)

Table 3.
The role of lipid-lowering therapy in Moyamoya disease.

pressure for Moyamoya patients with chronic hypertension should refer to which recommended in standard guidelines for hypertension. The fisrt-line antihypertensive drugs recommended by the guidelines include Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Calcium channel blockers and Diuretics [25]. Routine use of antihypertensive drugs in Moyamoya patients without hypertension for primary hemorrhagic or ischemic prevention is not recommended [22]. **Table 2** shows the role of antihypertensive treatment in Moyamoya disease.

2.3 The role of lipid-lowering therapy in Moyamoya disease

The benefit of lipid-lowering treatment in Moyamoya disease is unclear. There is no direct clinical trial regarding lipid-lowering therapy in Moyamoya disease. Among those lipid-lowering drugs, statins are the only sub-group that give benefit for primary and secondary ischemic stroke prevention in patients with presumed atherosclerotic disease [26, 27]. The indirect evidence from Church et al.'s study demonstrated that statins, the essential lipid-lowering drugs for atherosclerosis treatment, may reduce unilateral Moyamoya disease progression [28]. The Japanese guidelines for Moyamoya disease management do not recommend routine prescribing lipid-lowering treatment, except for presenting concurrent dyslipidemia [22]. It is reasonable to lower the low-density lipopretien (LDL) below 100 mg/dL as recommended in stroke patients with presumed atherosclerotic disease (**Table 3**).

3. Summary

Antiplatelet treatment with a single agent regimen is useful for Moyamoya patients with cerebral ischemia. There is no role of neither anticoagulant nor thrombolytic therapy in Moyamoya disease. Moyamoya patients with hypertension should get antihypertensive treatment. Experts do not recommend routinely prescribing antihypertensive drugs in Moyamoya disease without hypertension. Moyamoya patients with dyslipidemia may gain benefit from lipid-lowering therapy.

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