The Efficacy of Surgical Treatment for the Secondary Prevention of Stroke in Symptomatic Moyamoya Disease

**A Meta-Analysis**

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**Abstract:** The treatment of moyamoya disease (MMD) is controversial and often depends on the doctor’s experience. In addition, the choice of surgical procedure to treat MMD can differ in many ways. In this study, we performed a meta-analysis to determine whether surgical treatment of MMD is superior to conservative treatment and to provide evidence for the selection of an appropriate surgical treatment.

The human case–control studies regarding the association of MMD treatment were systematically identified through online databases (PubMed, Web of Science, Elsevier Science Direct, and Springer Link). Inclusion and exclusion criteria were defined for the eligible studies. The fixed-effects model was performed when homogeneity was indicated. Alternatively, the random-effects model was utilized.

This meta-analysis included 16 studies. Surgical treatment significantly reduced the risk of stroke (odds ratio (OR) of 0.17, 95% confidence interval (CI), 0.12–0.26, \( P < 0.01 \)). A subgroup analysis showed that surgical treatment was more beneficial to hemorrhagic MMD (OR of 0.23, 95% CI, 0.15–0.38, \( P < 0.01 \)), but there was no significant difference between surgical treatment and conservative treatment on ischemic MMD treatment (OR of 0.45, 95% CI, 0.15–1.29, \( P = 0.14 \)). Further analysis indicated that compared to direct bypass surgery, indirect bypass surgery had a lower efficacy on secondary stroke risk reduction (OR of 1.79, 95% CI, 1.14–2.82, \( P = 0.01 \)), while no significant difference was detected for perioperative complications.

Surgery is an effective treatment for symptomatic MMD patients, and direct bypass surgery may bring more benefits for these patients.

**INTRODUCTION**

Moyamoya disease (MMD) is a progressive stenosis or occlusion of the internal carotid artery (ICA) for unknown reasons. The most common clinical manifestation of MMD is ischemic or hemorrhagic stroke. The diagnosis is confirmed by angiographic examination with typical characteristics, such as stenosis or occlusion at the main branch of the ICA, and an abnormal vascular network at the skull base. Without intervention, MMD often leads to serious neurological defects or even death.

MMD treatment is controversial; therapy mainly depends on the doctor’s experience. Drugs such as aspirin are widely used, but the effect is not beneficial. Thus, surgery is frequently recommended. Extracranial–intracranial (EC-IC) bypass, which can be specified as direct anastomosis, indirect anastomosis, and combined, is the standard surgical treatment. In theory, EC-IC bypass can increase cerebral blood flow by improving abnormal neovascularization and preventing ischemic or hemorrhagic events. Some previous studies have suggested that surgery is superior to drugs alone. In contrast, Sundaram et al reported that conservative treatment results in a lower stroke recurrence rate and good functional outcomes.

Here, we performed a meta-analysis to evaluate the efficacy of surgical treatment versus conservative treatment on secondary stroke prevention and to analyze the impact of different surgical approaches on recurrent stroke prevention and perioperative complications.

**METHODS**

**Ethical Review**

The study was approved by the ethics committee of Second Affiliated Hospital of Zhejiang University School of Medicine.

**Literature Search**

We comprehensively searched eligible studies using several electronic databases, including PubMed, Web of Science, Elsevier Science Direct, and Springer Link. The key words used were “moyamoya disease,” “conservative treatment,” “surgical treatment,” “superficial temporal artery–middle cerebral artery anastomosis (SMA),” “SMA with encephalomyosynangiosis (EMS),” “SMA with encephaloduroarteriomyosynangiosis (EDAS),” “SMA with encephaloduroarteriosynangiosis (EDAMS),” “direct bypass surgery,” “indirect bypass surgery,” “secondary stroke,” and “perioperative complication.” All
papers published until June 2015 were included. Additionally, reference lists in the identified publications and the main electronic sources of ongoing trials were also examined. Two authors (JRL and JYC) independently evaluated the search results by reading the titles, and 2 other reviewing authors (CQ and XBY) independently reviewed the abstracts of the initially screened papers, with disagreement settled by senior authors (LW and GC).

Our criteria for including studies was as follows: patients had a digital subtraction angiography (DSA) confirmation of symptomatic MMD, for example, ischemic or hemorrhagic stroke, transient ischemic attack (TIA), or seizure; randomized controlled trials (RCTs), prospective controlled cohort studies and retrospective case-controlled studies; quality score > 5 on the Newcastle-Ottawa Scale (NOS). 10 The exclusion criteria were as follows: a system review or case report; the study was not written in English; only the abstract of a study was available; studies in which participants presented with secondary ICA stenosis or occlusion (atherosclerosis, posttraumatic, etc.).

Data Abstraction
Two review authors (CQ and XBY) independently extracted data using a uniform standardized form until an agreement was reached. The primary outcome was recurrent ischemic or hemorrhagic stroke after intervention in the follow-up period (more than 6 months). The secondary outcome was perioperative complications, such as ischemic or hemorrhagic events, seizure, hyperperfusion syndrome, ischemic wound healing, and perioperative death. Other related factors, such as population characteristics and surgical procedures, were also extracted.

Statistical Analysis
Data were processed in Review Manager Version 5.3 from the Cochrane Collaboration. Dichotomous variables were presented as an odds ratio (OR) with a 95% confidence interval (CI). If the I² value, which indicated the heterogeneity, was less than 50%, a fixed effect model was used; otherwise, a random effect model was adopted. A p < 0.05 was considered signifi-
cant for all analysis. In addition, funnel plots were generated to detect a potential publication bias.

**RESULTS**

**Literature Selection and Characteristics**

The detailed search process is illustrated in the flow chart (Fig. 1). We retrieved 2103 records after the initial search strategy, and 24 records were kept for further analysis after scanning the title and abstract. Then, 8 records were excluded for no data. Finally, 16 articles were included, which 8 articles compared the efficacy of conservative versus surgical treatment in 961 patients, 12 studies compared the recurrent stroke rate of indirect and direct bypass surgery in 837 patients and 11 papers focused on surgical complications after indirect and direct bypass surgery in 1071 patients. Additionally, the mean NOS score was 6.9 indicating that the methodological quality of studies was good (Table 1). For all analyses pertaining to efficacy and acceptability, heterogeneity was detected in subgroup analysis of ischemic MMD and a random effect model was used. There was no heterogeneity detected in the other analyses.

**The Efficacy of Surgical Treatment for Stroke Prevention in Moyamoya Disease**

Nine hundred sixty-one patients from 8 studies were included (692 patients received surgery and 269 patients received conservative treatment). In this analysis, surgical treatment of MMD showed significant efficacy in recurrent stroke prevention (OR of 0.17, 95% CI, 0.12–0.26, \( P < 0.01 \), \( I^2 = 33\% \)) (Fig. 2A). In the hemorrhagic MMD subgroup analysis, total 610 patients were included (377 patients received surgery and 233 had conservative treatment), and surgical treatment showed a significant efficacy of rebleeding prevention (OR of 0.23, 95% CI, 0.15–0.38, \( P < 0.01 \), \( I^2 = 1\% \)) (Fig. 2B). However, the advantage of surgical treatment was not significantly better than conservative treatment for ischemic MMD patients (OR of 0.53, 95% CI, 0.02–11.13, \( P = 0.14 \), \( I^2 = 85\% \)) (Fig. 2C). No publication bias was found in the funnel plot (Fig. 4A).

**The Efficacy and Safety of Indirect Bypass or Direct Bypass Surgery in Moyamoya Disease Treatment**

Eight-hundred thirty-seven patients from 12 studies were analyzed (301 patients received indirect surgery and 536 patients received direct or combined surgery). For recurrent stroke prevention, direct or combined surgery showed a significant efficacy (OR of 1.79, 95% CI, 1.14–2.84, \( P = 0.01 \), \( I^2 = 28\% \)) (Fig. 3A). For surgical complication analysis, 1071 patients from 11 studies were included (425 patients received indirect bypass surgery and 646 patients received direct or combined bypass surgery), but no significant difference was found between the 2 groups (OR of 0.8, 95% CI, 0.58–1.11, \( P = 0.18 \), \( I^2 = 19\% \)) (Fig. 3B). No publication bias was found in the funnel plot (Fig. 4B and C).

**DISCUSSION**

At present the natural history MMD is unclear due to a low incidence and the clinical course changes with age and race, thus treatment mainly depends on a doctor’s experience. To our knowledge a meta-analysis has not been used to estimate the efficacy and safety of MMD treatment, and only 1 randomized controlled trial (RCT) was conducted on hemorrhagic MMD. Most studies of MMD treatment are retrospective and lack control. In our meta-analysis, we gathered high quality research on MMD treatment and found meaningful results.

We found that surgical treatment on symptomatic MMD had a lower secondary stroke rate than conservative treatment (15.9% (110/692) vs. 43.5% (117/269), OR of 0.17, \( P < 0.01 \), \( I^2 = 33\% \)) (Fig. 2). However, the advantage of surgical treatment was not significantly better than conservative treatment for ischemic MMD patients (OR of 0.53, 95% CI, 0.02–11.13, \( P = 0.14 \), \( I^2 = 85\% \)) (Fig. 2C). No publication bias was found in the funnel plot (Fig. 4A).

**TABLE 1. Main Characteristics of Studies Included in This Meta-Analysis**

| Author      | Year | Country | Ethnicity | Sample Size (n) | NOS Score |
|-------------|------|---------|-----------|----------------|-----------|
| Hallemeier11 | 2006 | USA     | Caucasian | 34             | 6         |
| Mesiwala12  | 2008 | USA     | Caucasian | 39             | 6         |
| Ohue13      | 2008 | Japan   | Asian     | 17             | 6         |
| Bang14      | 2011 | Korea   | Asian     | 65             | 8         |
| Czabanka14  | 2011 | Germany | Caucasian | 30             | 7         |
| Han15       | 2011 | Canada  | Caucasian | 39             | 7         |
| Bradley24   | 2012 | USA     | Caucasian | 45             | 7         |
| Choi17      | 2012 | Korea   | Asian     | 43             | 7         |
| Kim18       | 2012 | Korea   | Asian     | 96             | 8         |
| Lee8        | 2012 | Korea   | Asian     | 142            | 6         |
| Liu20       | 2012 | China   | Asian     | 97             | 7         |
| Choi19      | 2013 | Korea   | Asian     | 44             | 6         |
| Oyama21     | 2013 | Japan   | Asian     | 30             | 7         |
| Miyamoto22  | 2014 | Japan   | Asian     | 80             | 9         |
| Huang23     | 2015 | China   | Asian     | 154            | 8         |
| Liu7        | 2015 | China   | Asian     | 528            | 6         |

NOS = Newcastle-Ottawa Scale.
of the biggest obstacles. In the subgroup analysis of hemorrhagic MMD, surgical treatment had a lower rebleeding rate than conservative treatment (10.6% (40/377) vs. 31.8% (74/233), OR of 0.24, \( P < 0.01 \)), which suggests that the bypass surgery was more suitable for hemorrhagic MMD. However, no significant difference of secondary stroke rate was detected in the ischemic MMD subgroup (17.9% (20/112) vs. 17.4% (8/46), OR of 0.53, \( P = 0.68 \)), which completely opposes the view of most doctors. Considering that there were only 2 studies included an ischemic MMD analysis, we should interpret this result carefully. In addition, we cannot easily conclude that surgical treatment is no more beneficial than conservative treatment in ischemic MMD patients. Future larger prospective trials may solve this problem. Clinical course of MMD is different between pediatric and adult MMD patients, and previous studies reported that conservative treatment resulted in poor outcomes for pediatric and adult MMD patients.\(^{25,26}\) However, we could not perform subgroup analysis due to insufficient data. As for asymptomatic MMD, medical treatment is often suggested because of the low rate of symptomatic progression (5.3%),\(^{27}\) but if these patients presented with reduced vascular reserve or smoking, surgical treatment resulted in fewer cerebrovascular events.\(^{28,29}\) Unfortunately, due to insufficient data, we could not perform this subgroup analysis.

Currently there are at least seven different surgical methods for MMD, which can be group into either a direct or indirect bypass surgery approach. SMA, SMA with EMS, SMA with EDAS, and SMA with EDAMS are direct bypass surgery approaches. EMS, EDAS, and multiple cranial bur holes are indirect bypass surgery approaches. In this meta-analysis, indirect bypass surgery showed a higher secondary stroke rate than direct bypass surgery (15.0% (45/301) vs. 8.6% (46/536), OR of 1.79, \( P = 0.01 \)), but for perioperative complications there was no significant difference between indirect and direct bypass surgery (10.4% (44/425) vs. 15.8% (102/646), OR of 0.76, \( P = 0.19 \)). These findings suggest that direct bypass surgery is superior to indirect bypass surgery for secondary stroke prevention. Although direct bypass surgery was more beneficial to MMD treatment, this approach is more difficult technically for several reasons, including improper donor or recipient vessels, hyperperfusion, and longer operation time. Finding appropriate donor and recipient vessels is a major problem for direct bypass surgery. Currently some neurosurgeons used virtual surgical planning for SMA surgery with 3-dimensional DSA or magnetic resonance angiography (MRA), which is easier.\(^{30,31}\) Moreover, direct bypass surgery might lead to symptomatic cerebral hyperperfusion postoperatively, and some studies have demonstrated that prophylactic blood pressure lowering can significantly reduce the incidence of...
symptomatic cerebral hyperperfusion. Finally, to circumvent the poor scalp wound healing that often occurs with direct or combined bypass surgery, Kuroda et al modified the STA surgical dissection technique. Although direct bypass surgery has improved a lot, it is still unfit for many MMD patients, and indirect bypass surgery remains an important alternative treatment.

In order to facilitate a better understanding of the effect estimations, several limitations of this analysis should be noted. Most of the studies in this meta-analysis were retrospective and only 1 RCT was available. Therefore, more strictly designed studies are urgently needed. Only a few studies presented clear inclusion and exclusion criteria, and each study was conducted with different objectives. Differences in the diagnostic criteria and operative technique between the different hospitals of each study we analyzed might have led to inconsistent results. Detailed data on perioperative complications were insufficient, and thus an advanced analysis could not be implemented.

In conclusion, surgical treatment reduced the risk of recurrent stroke in symptomatic MMD patients, especially in hemorrhagic MMD patients. In addition, compared to indirect bypass surgery, direct bypass surgery showed a lower secondary stroke rate and a similar perioperative complication rate. Based on these results, we recommended direct bypass surgery as the first choice for symptomatic MMD patients for a lower recurrent stroke risk. However, perioperative complication and the
demanding nature of this surgical technique are important obstacles to consider for the treatment of MMD. Additional researches of these aggravating factors are critically important.

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