Direct versus indirect revascularization procedures for moyamoya disease: a comparative effectiveness study

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OBJECTIVE Moyamoya disease (MMD) is a chronic cerebrovascular disease that can lead to devastating neurological outcomes. Surgical intervention is the definitive treatment, with direct, indirect, and combined revascularization procedures currently employed by surgeons. The optimal surgical approach, however, remains unclear. In this decision analysis, the authors compared the effectiveness of revascularization procedures in both adult and pediatric patients with MMD.

METHODS A comprehensive literature search was performed for studies of MMD. Using complication and success rates from the literature, the authors constructed a decision analysis model for treatment using a direct and indirect revascularization technique. Utility values for the various outcomes and complications were extracted from the literature examining preferences in similar clinical conditions. Sensitivity analysis was performed.

RESULTS A structured literature search yielded 33 studies involving 4197 cases. Cases were divided into adult and pediatric populations. These were further subdivided into 3 different treatment groups: indirect, direct, and combined revascularization procedures. In the pediatric population at 5- and 10-year follow-up, there was no significant difference between indirect and combination procedures, but both were superior to direct revascularization. In adults at 4-year follow-up, indirect was superior to direct revascularization.

CONCLUSIONS In the absence of factors that dictate a specific approach, the present decision analysis suggests that direct revascularization procedures are inferior in terms of quality-adjusted life years in both adults at 4 years and children at 5 and 10 years postoperatively, respectively. These findings were statistically significant ($p < 0.001$ in all cases), suggesting that indirect and combination procedures may offer optimal results at long-term follow-up.

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KEY WORDS moyamoya; revascularization; direct; indirect; decision analysis; vascular disorders

MOYAMOYA disease (MMD) is a rare, chronic disorder of unknown etiology defined by the gradual occlusion of intracranial vessels, beginning with the supraclinoid carotid arteries and progressing to the anterior, middle, and posterior cerebral arteries. As these vessels become occluded, small collaterals form at the base of the brain, which together give the appearance of a “puff of smoke” on angiographic studies.^{59,60} This disease, which is well documented in Asian populations, has a varying presentation depending on the age of the patient and classically manifests with intracerebral hemorrhage in

adults and ischemic stroke in children.¹⁴ The natural history of this disease is also devastating, leading to recurring strokes and subsequent neurocognitive decline.^{2,4,41}

The treatment prospects for an individual with MMD are limited because no known medical therapy has proven to be effective.^{5,16} Surgical approaches have been developed to directly restore perfusion to oxygen-deprived areas of the brain or indirectly to enable collateral vessel formation. Surgical intervention has been demonstrated to reduce ischemic events and thus has become the only form of effective treatment in symptomatic MMD.^{5,22}

ABBREVIATIONS MMD = moyamoya disease; QALY = quality-adjusted life year; QOL = quality of life.

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Direct techniques, commonly involving a superficial temporal artery (STA) to middle cerebral artery (MCA) bypass, have been successfully used since the 1970s.⁴⁸ Direct revascularization techniques are the most efficacious at reducing ischemic events.^{23,43} However, these techniques also have a myriad of drawbacks.

Direct revascularization carries the risk of hyperperfusion syndrome, which results from a sudden increase in cerebral blood flow; the incidence is as high as 28% and is seen most often in patients with extensive preoperative ischemia.^{11–13,23} Hyperperfusion syndrome can result in a temporary clinical picture that includes sensorimotor loss, aphasia, and dysarthria.⁴⁸ Furthermore, direct procedures can accelerate stenosis of the internal carotid artery (ICA) as well the growth of moyamoya collaterals, which can lead to frontal lobe infarcts and cheiro-oral syndrome.^{20,40,54} Lastly, the procedure is challenging in the pediatric population because of the patients' smaller, more delicate cerebral vasculature.³⁷

Indirect techniques rely on tissue supplied by the external carotid artery, which is placed on the brain surface and promotes angiogenesis. This approach generally requires less operative time since it is both technically less challenging and less invasive.⁶⁴ Importantly, the indirect approaches do not require temporary occlusion of MCA branches, which is required in the STA-MCA bypass. As such, indirect approaches have a better safety profile than direct procedures and are preferred in children and adults with other medical comorbidities.^{4,9} However, in stark contrast to children, collaterals only form in approximately half of the adult patients following the indirect procedures.⁴⁴ Even then, collaterals take months to mature, while the direct procedures provide robust reperfusion immediately.^{19,20,53} Immediate reperfusion can pose a risk of symptomatic hyperperfusion or postoperative hemorrhage in a chronically ischemic brain. Following indirect procedures, collaterals will only form in the area of the craniotomy field, and a field of insufficient size may lead to persistent frontal lobe ischemia.³⁸

Combined procedures have also been employed by some surgeons who have postulated that the technique reduces the incidence of repeat bleeding; however, there is little evidence to show if the outcomes are actually improved or potentially worsened.^{29,39} Thus, the literature does not present a clearly superior revascularization technique in the surgical management of MMD. There have been no randomized clinical trials to facilitate comparison; furthermore, many studies to date combine adult and pediatric data when reporting outcomes.⁵⁸ Hence, in this report, we use a decision analytical model to compare clinical outcomes of direct, indirect, and combined revascularization techniques in pediatric and adult patients with MMD.

Methods

We developed a decision analytical model to compare clinical outcomes of direct and indirect revascularization techniques in pediatric and adult patients with MMD. The model projects quality-adjusted life years (QALYs) for the number of postoperative years for which adequate follow-

up data are available. Data for the model were derived from a critical review of published reports.

Management Strategies and Outcomes

Direct revascularization involves STA-MCA (or other high-flow arterial) bypasses, whereas indirect bypasses involve placing tissue vascularized by extracranial vessels on the brain surface to promote revascularization. Indirect procedures include encephaloduroarteriosynangiosis, encephaloduroarteriomyosynangiosis, and pial synangiosis. Finally, combined approaches involve both direct and indirect procedures in the same patient.

Outcome is measured by surgery's impact on the patient's health-related quality of life (QOL). This is customarily measured as utility, a parametric 0–1 scale of a given outcome's effect on QOL. These are patients' relative preferences for a given health outcome.⁵⁷ For example, an uneventful outcome (no perioperative complications or late-onset strokes) would be scored 1, and death would receive a score of 0. Adverse outcomes would receive intermediate scores. To allow for the possibility that the rate of late strokes would increase with duration of follow-up, we employed QALYs, a combination of both quality and QOL. As an example, 5 years without operative or delayed complications would rate 5 QALYs as would 10 years during which the patient's QOL was 0.5. We assume that perioperative strokes influence utility for the entire follow-up, whereas late-onset strokes occur, on average, midway through the follow-up period.

Decision Analytical Model

Regardless of the surgery chosen, there may be perioperative complications, each with an impact on QOL. During follow-up, delayed ischemic stroke or intracranial hemorrhage may occur. For a given type of surgery, each pathway and outcome is dealt with in the model (Fig. 1). The probabilities and utilities of each outcome are calculated to arrive at an expected utility for each treatment option.

Data Collection and Management

We searched Medline, EMBASE, and the Cochrane Library for articles containing the key word "moyamoya" in conjunction with either the key word "therapy" or "surgery." We limited our search to articles published in English between 1990 and February 2013. All articles were reviewed by at least 2 authors. The search yielded 695 articles, of which 33 were used in the analysis. These series reported on 4197 surgeries. Reasons for article exclusion are summarized in Fig. 2. Separate searches were done to determine utilities associated with ischemic stroke and intracranial hemorrhage. Pediatric and adult (mean age > 20 years) series were separated for the purpose of analysis. When more than one age group or surgical technique was reported in the same publication, we separated the groups. When this was impossible, the article was excluded from analysis. Table 1 summarizes the articles included in this study. In the absence of any controlled trials, all must be considered Class IV evidence.³ For both pediatric and adult groups, we separately recorded the following: numbers of sides operated upon in each series, mean ages,

FIG. 1. Decision analytical tree outlining possible pathways and outcomes after surgery for MMD. After surgery, a patient can have an unremarkable recovery, or suffer perioperative stroke, intracranial hemorrhage, or even death. These same 4 possible outcomes can occur during follow-up.

sex distribution, perioperative complications and deaths, mean length of follow-up, late ischemic or hemorrhagic strokes or deaths. There was only a single report of combined revascularization in adults, so this category was omitted from the analysis. The patient population did not undergo subgroup analysis for Caucasian and Asian populations due to low numbers in relevant studies.

Statistical Analysis

Probabilities report the likelihood that a hypothetical patient travels along a particular pathway picture in Fig. 1. These represent point estimates of pooled data, which were determined via meta-analysis.¹⁰ After testing to exclude heterogeneity,³⁶ an inverse-variance-weighted random-effects model was used to calculate means and distributions. Demographic data, such as mean ages and

TABLE 1. Articles used in the analysis

Authors & Year	Age Group	Bypass Technique	No. of Cases
Adelson & Scott, 1995	Pediatric	Indirect	34
Choi et al., 1997	Pediatric	Direct	56
	Pediatric	Indirect	56
Darwish & Besser, 2005	Pediatric	Direct	7
	Pediatric	Indirect	10
	Pediatric	Combined	5
Duan et al., 2012	Adult	Direct	45
	Adult	Indirect	1229
Fujimura et al., 2008	Pediatric	Combined	17
Hankinson et al., 2008	Pediatric	Indirect	12
Hirotsune et al., 1997	Pediatric	Indirect	13
Hyun et al., 2010	Adult	Indirect	228
Ishikawa et al., 1997	Pediatric	Indirect	5
	Pediatric	Combined	62
Ishikawa et al., 2006	Adult	Combined	11
	Pediatric	Combined	15
Isono et al., 2002	Pediatric	Indirect	22
Jea et al., 2005	Pediatric	Indirect	28
Karasawa et al., 1992	Pediatric	Combined	104
Kashiwagi et al., 1997	Pediatric	Indirect	25
Khan et al., 2012	Adult	Direct	717
Kim et al., 2000	Pediatric	Indirect	171
Kim et al., 2002	Pediatric	Indirect	92
Kim et al., 2003	Pediatric	Indirect	134
Kim et al., 2007	Pediatric	Indirect	16
	Pediatric	Combined	7
Kim et al., 2010	Pediatric	Indirect	410
Mukawa et al., 2012	Pediatric	Indirect	172
Nagata et al., 2006	Pediatric	Indirect	15
Ohtaki et al., 1998	Pediatric	Combined	16
Park et al., 2007	Pediatric	Indirect	34
Phi et al., 2011	Pediatric	Indirect	65
Robertson et al., 1997	Pediatric	Indirect	25
Sainte-Rose et al., 2006	Pediatric	Indirect	25
Sakamoto et al., 1997	Pediatric	Combined	19
Scott et al., 2004	Pediatric	Indirect	126
Song et al., 2012	Pediatric	Indirect	36
Starke et al., 2009	Adult	Indirect	67
Touho, 2007	Pediatric	Direct	53
	Pediatric	Combined	13

sex distributions, were pooled in the same fashion. We tested the hypothesis that late stroke and hemorrhage rates were linearly related to length of follow-up. For this, we employed an inverse-variance-weighted random-effects model of meta-regression. These data were used to calculate expected QALYs associated with each of the 3 surgical options. Sensitivity analysis used beta distributions for probabilities, normal distribution for utilities, and a 2D Monte Carlo simulation (100 trials, each made up of 100

FIG. 2. Summary of the structured literature review showing numbers of abstracts reviewed, articles read, those used in our analysis, and reasons for rejection.

microsimulations).⁶ Meta-analytical pooling and meta-regressions were done with Stata (version 12.1, StataCorp LP). Analyses of the model employed TreeAge Pro 2012 (Tree Age Software, Inc.). Statistical comparisons employed one-way ANOVA; pairwise comparisons used the Bonferroni correction for multiple comparisons. We considered differences whose $p < 0.05$ to be significant.

Results

The utility of a generic ischemic stroke is 0.599 ± 0.364 ;¹⁵ that of intracranial hemorrhage is 0.868 ± 0.169 .⁴²

Pediatric MMD

Table 2 presents mean ages and sex distributions for the 3 pediatric surgical cohorts. There were no significant differences among the 3 groups, nor were there any significant differences between any 2 pairs.

Pooled values of probabilities for the model are presented in Table 3. Meta-regression showed no significant increased rate of stroke or hemorrhage with length of follow-up. Accordingly, the pooled values of these parameters were used. So few studies reported mortality rates during follow-up that this aspect was excluded from the analysis. It is expected that perfect treatment, without perioperative or late complications, would result in a number of QALYs equal to the length of the follow-up.

The model calculated the expected QALYs in the 3 pediatric groups after 5- and 10-year follow-up periods (Table 4). These differences were highly significant ($F = 209.04$, $p < 0.001$). Although there is no significant difference between the combined and indirect approaches at 5 or 10 years ($p = 0.383$ and $p = 0.261$, respectively), both were superior to direct revascularization ($p < 0.001$).

Adult MMD

Table 2 also presents mean ages and sex distributions for the 2 adult surgical cohorts. The Student t-test shows no significant differences between the groups. Pooled values of probabilities for the model are presented in Table 3. As in the case of children, meta-regression showed no significant increased rate of stroke or hemorrhage with length of follow-up. We used pooled values here as well. Late death occurred in $0.8\% (\pm 0.01)$ of adults.

Because so few reports involved follow-up exceeding 4 years postsurgery, we compared procedures at that point. Table 4 shows that indirect revascularization resulted in over one-half QALY more than the direct option during the 4-year follow-up period. This difference was highly significant ($p < 0.001$).

Discussion

In this study, we applied decision analysis methodology to compare the effectiveness of surgical revascularization techniques to treat MMD. To date, there have been no clinical trials comparing surgical revascularization techniques for MMD. Were an adequately powered, well-run, randomized, controlled trial practical, it would be preferable to a comparative effectiveness study such as ours. However, the large numbers of subjects needed, the lack of clinical equipoise among neurosurgeons, the great variety of surgical techniques, and clinical presentation in MMD make such a trial very unlikely. Thus, our results currently offer the best comparison of the two approaches. The present study shows that in pediat-

TABLE 2. Average ages and proportion of females in surgical groups

Age Group	Mean Age	SD	Difference	Proportion Female	SD	Difference
Children						
Direct	10.037	4.868	F = 1.888, p = 0.168	0.579	0.198	F = 1.003, p = 0.379
Indirect	8.599	1.965		0.589	0.067	
Combined	7.439	1.264		0.641	0.119	
Adults						
Direct	29.7	2.020	p = 0.334	0.607	0.151	p = 0.914
Indirect	34.7	6.362		0.624	0.1544	

TABLE 3. Pooled values of probabilities for the model

Age Group	Perioperative Complication						Late Complication			
	Mortality		Ischemic Stroke		Intracranial Hemorrhage		Ischemic Stroke		Intracranial Hemorrhage	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Children										
Direct	0	0	0.096	0.042	0.018	0.004	0.478	0.463	0.119	0.218
Indirect	0.010	0.009	0.090	0.078	0.029	0.057	0.115	0.064	0.080	0.061
Combined	0.010	0.003	0.058	0.053	0	0	0.158	0.097	0.046	0.032
Adults										
Direct	0.011	0.003	0.037	0.039	0.017	0.003	0.014	0.047	0.018	0.033
Indirect	0	0	0.050	0.029	0.001	0.000	0.105	0.080	0.016	0.0002

ric patients, there was no significant difference between the combined and indirect approaches, but both are superior to direct revascularization at 5- and 10-year follow-up periods. In adults, indirect revascularization yielded 50% more QALYs than the direct approach at the 4-year follow-up point.

This apparent superiority of indirect procedures may be due to the sheer technical difficulty of the direct procedures and the learning curves associated with performing them well. Though direct procedures may be more effective in reducing the incidence of future stroke, the added risk of the procedure's technical difficulty (especially in children), hyperperfusion syndrome, and increasing the rate of stenosis appear to outweigh this benefit. The reduced operative time and invasiveness, as well as the relative ease of the indirect procedures, may contribute to the well-documented decrease in adverse effects. Moreover, it is also possible that the risk of perioperative stroke from the delayed formation of collaterals following indirect procedures may be overstated. It is also important to note that appropriate propensity matching is not possible given that the patient populations may differ.

Our study noted that pediatric patients tolerated the combined procedure well and did not suffer from an increased rate of adverse events as compared with adult patients undergoing the direct procedure. However, the current study is a review rather than a study designed to test noninferiority. It would be necessary to conduct further analysis to compare the indirect and combined procedure in the pediatric population to determine truly if the outcomes were similar. If the two procedures were determined to have equal efficacy, it stands to reason that the choice would be the less invasive approach.

Our decision model is limited by its simplifying as-

sumptions. Our small numbers precluded us from confirming that the incidence of late-onset postoperative ischemic stroke increases over time. Additionally, particular surgeons are certainly more facile at direct anastomoses than others, and certain indirect procedures may well be superior to others. The model developed in the present study cannot make allowances for this. Furthermore, we limited surgical complications to ischemic stroke and intracranial hemorrhage. However, it should be noted that other recorded complications tended to be transient or mild with little effect on overall outcome.

An important limitation in a retrospective analysis such as this is the unknown, potentially confounding factors that influenced selections of surgical approach in the studies that were analyzed and used to create our decision model. Hence, we were unable to control for various vascular factors that might have influenced a surgeon's decision making, and likewise, we could not ensure that these factors were the same among the various studies reviewed. This may have introduced selection bias and thus have restricted the validity of our results. Finally, many studies of outcome after revascularization have only focused on ischemic events, whereas other adverse outcomes such as seizures and neurocognitive decline are also critical considerations.⁶³

Conclusions

We performed a comparative analysis of direct, indirect, and combined revascularization techniques for MMD in adults and children. In both patient populations, we found significantly inferior outcomes with direct revascularization compared with the other two surgical approaches.

TABLE 4. Comparison of expected QALYs in children and adults

Surgical Strategy	Follow-Up Durations					
	Children, 5 Yrs		Children, 10 Yrs		Adults, 4 Yrs	
	Mean	SD	Mean	SD	Mean	SD
Direct	4.0560	0.1253	8.1177	0.1710	3.502	0.081
Indirect	4.3143	0.1274	8.6523	0.1954	3.553	0.059
Combined	4.3461	0.1222	8.7090	0.1986	NA	NA

NA = not analyzed (inadequate data).

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Disclosures

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Author Contributions

Conception and design: Stein, Macyszyn, Ali. Acquisition of data: Macyszyn, Attiah, Faught, Hossain, Man, Patel, Sobota. Analysis and interpretation of data: Macyszyn, Ali. Drafting the article: Macyszyn, Attiah, Ali, Zager. Critically revising the article: Stein, Macyszyn, Ali, Zager. Reviewed submitted version of manuscript: Stein, Macyszyn, Ma, Ali. Approved the final version of the manuscript on behalf of all authors: Stein. Statistical analysis: Macyszyn, Ali. Administrative/technical/material support: Stein, Macyszyn, Attiah. Study supervision: Stein, Macyszyn, Zager.

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