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Reduction in overt and silent stroke recurrence rate following cerebral revascularization surgery in children with sickle cell disease and severe cerebral vasculopathy

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Abstract

Background—Children with sickle cell disease (SCD) and moyamoya may benefit from indirect cerebral revascularization surgery in addition to chronic blood transfusion therapy for infarct prevention. We sought to compare overt and silent infarct recurrence rates in children with SCD undergoing revascularization.

Methods—This was a retrospective cohort study of all children with SCD and moyamoya treated at two children's hospitals. Clinical events and imaging studies were reviewed.

Results—Twenty-seven children with SCD and confirmed moyamoya receiving chronic transfusion therapy were identified, of whom 12 underwent indirect cerebral revascularization. Two subjects had post-operative transient ischemic attacks and another had a subarachnoid blood collection, none of which caused permanent consequences. Two subjects had surgical wound infections. Among these 12 children, the rate of overt and silent infarct recurrence decreased from 13.4 infarcts/100 patient-years before revascularization to 0 infarcts/100 patient-years after revascularization (p=0.0057); the post-revascularization infarct recurrence rate was also significantly lower than the overall infarct recurrence of 8.87 infarcts/100 patient-years in 15 children without cerebral revascularization (p=0.025).

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All authors declare no relevant conflicts of interest.

Conclusion—The rate of overt and silent infarct recurrence was significantly lower following indirect cerebral revascularization. A prospective study of cerebral revascularization in children with SCD is needed.

Keywords

stroke; sickle cell anemia; pediatric; moyamoya; cerebral vasculopathy

Introduction

Children with sickle cell disease (SCD) have approximately 250 times greater risk for strokes than the general pediatric population.[1,2] The historical prevalence of overt stroke was approximately 11% in those with hemoglobin (Hb) SS disease by age 20 years.[2] Chronic blood transfusion therapy is the standard therapy for primary and secondary prevention of stroke in children with SCD, reducing the risk of first stroke by 90%[3] and of recurrent stroke from approximately 70% to 20%.[4,5] Chronic transfusion therapy does not eliminate stroke risk, however. Recurrent stroke rates despite chronic transfusion therapy range from 2.0 overt plus silent strokes/100 patient-years in children with a history of silent strokes[6] to 8.1 overt plus silent strokes/100 patient-years in those with prior overt strokes.[7]

Moyamoya is a continuum of progressive large vessel cerebral vasculopathy, characterized by stenosis and occlusion of arteries of the circle of Willis with eventual collateral vessel formation. It occurs spontaneously or in the context of systemic disorders, causing recurrent cerebral infarctions, transient ischemic attacks (TIAs), and cerebral hemorrhages. Moyamoya syndrome and progressive cerebral vasculopathy are prevalent in children with SCD and overt strokes despite chronic transfusion therapy and are a significant cause of recurrent silent and overt strokes. In a retrospective cohort study, the presence of moyamoya collateral vessels conferred a relative risk of recurrent overt stroke of 2.4,[8] while children with progressive cerebral vasculopathy, including progressive arterial stenosis or moyamoya collateral vessels, had a relative risk of recurrent overt or silent infarction of 12.7 in a prospective cohort study.[7]

Based on experience in children with non-SCD moyamoya, many centers perform cerebral revascularization in children with SCD and moyamoya, typically an indirect revascularization approach.[9,10] Indirect revascularization, including the commonly-used pial synangiosis technique, relies on ingrowth of new collateral vessels into the brain tissue and typically results in symptomatic improvement within several weeks to months post-operatively. In pial synangiosis, an intact segment of the superficial temporal artery is mobilized, and a bone flap is created. The dura and arachnoid are opened and the intact superficial temporal artery segment is sutured to the pial surface, without cutting or clamping the artery at either end. Finally, grooves are cut in the bone flap to accommodate the arterial segment, and the flap is replaced.[10–12] While several case series suggest that pial synangiosis is safe in children with SCD and moyamoya syndrome and reduces their risk of recurrent overt strokes,[9] its effect on silent cerebral infarctions (SCIs) has not been determined. We undertook a two-center retrospective cohort study to determine the

neurologic outcomes of children with SCD and moyamoya syndrome on chronic transfusion therapy who underwent cerebral revascularization surgery compared with those on chronic transfusion therapy who did not undergo cerebral revascularization. We hypothesized that cerebral revascularization surgery reduces silent and overt infarct recurrence in children with SCD and moyamoya syndrome when compared to children who do not undergo cerebral revascularization surgery.

Methods

A retrospective cohort study was performed at two academic centers, Riley Hospital for Children at Indiana University Health and St. Louis Children's Hospital/Washington University School of Medicine, of patients with SCD and severe cerebral vasculopathy. At both sites, patients with overt strokes or cerebral vasculopathy undergo surveillance brain magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) studies approximately annually to monitor for development of new infarcts or progressive cerebral vasculopathy. Cerebral revascularization, typically via pial synangiosis,[12] is offered to all patients with severe cerebral arterial stenosis or occlusion (as determined by digital subtraction angiography or computed tomography angiography) with or without moyamoya collateral vessel formation and regardless of cerebral infarcts or TIAs. Both centers follow the perioperative guidelines published by Smith et al,[13] including goal perioperative Hb concentration of 10 to 11 g/dL and Hb S <30%. Aspirin is prescribed to all children prior to revascularization surgery at both sites and is continued through the perioperative period. Following revascularization surgery, all children continue aspirin indefinitely. Aspirin is also prescribed to some children with severe vasculopathy/moyamoya who do not undergo cerebral revascularization surgery at their physician's discretion. Additionally, all patients continue chronic blood transfusion therapy postoperatively, unless they receive a hematopoietic stem cell transplant (HSCT).

Patients at both medical centers who received chronic transfusion therapy between 2000 and 2014 due to abnormal transcranial Doppler ultrasonography (TCD) or overt or silent stroke were reviewed. For inclusion, we required that severe cerebral vasculopathy be described in the clinical reports of two or more MRI studies or confirmed on conventional angiogram or computed tomography (CT) angiogram, since turbulent blood flow may cause the artifactual appearance of arterial stenosis on time-of-flight MRA.[14] Exclusion criteria were incomplete medical records, lack of confirmation of severe cerebral vasculopathy on two imaging studies, and lack of chronic blood transfusion therapy. Institutional Review Board approval with waiver of informed consent was obtained at both sites.

Two investigators (E.M.H. and M.L.H.) reviewed all available medical records at Riley Hospital for Children at Indiana University Health and St. Louis Children's Hospital for the following data: patient demographics; dates and symptoms of all strokes; date of and reason for initiation of chronic transfusion therapy; Hb S percentage goal for transfusion therapy; treatment with aspirin; dates and results of all brain imaging studies; dates, laterality, and outcomes of cerebral revascularization procedures; duration of follow-up; and date of hematopoietic stem cell transplant. New infarcts and cerebral vasculopathy progression were determined by reviewing clinically reported results of brain MRI/MRAs. Overt strokes were

defined as new neurological symptoms either lasting greater than 24 hours or having an area of diffusion restriction or a T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensity on MRI that was consistent with the neurological findings; SCIs were defined as T2 or FLAIR hyperintensities on brain MRI that did not correlate with any reported neurological symptoms. Severe cerebral vasculopathy was defined as occlusion or near-occlusion of the internal carotid or middle cerebral arteries on clinically reported MRAs, CT angiograms, or conventional angiograms, with or without the presence of moyamoya collateral vessels. TIAs were defined as acute neurological symptoms lasting less than 24 hours, typically hemiparesis or hemisensory loss, that did not have a correlating new area of diffusion restriction or T2 or FLAIR hyperintensity on MRI. Study data were collected and managed using REDCap electronic data capture tools hosted at Washington University School of Medicine.[15]

Statistical Methods

Categorical variables were compared using Fisher's exact test, and continuous variables were analyzed using non-parametric tests. Incidence rates were compared with Poisson distribution. The level of significance was specified as <0.05. The Bejamini-Hochberg procedure was used, with a false discovery rate of 0.05.[16] SPSS version 21 (IBM, Armonk, NY) was used for statistical analysis.

Results

Forty children were identified with SCD and potential severe cerebral vasculopathy, of whom 13 were excluded (lack of imaging confirmation in eight, lack of chronic transfusion therapy following diagnosis of stroke in three, and inadequate medical records in two). Despite incomplete clinical and imaging records, the excluded children were severely affected, with 6 of 13 having recurrent silent or overt strokes or TIAs while receiving chronic transfusion therapy or HSCT. Twenty-seven children met all inclusion criteria; 15 (56%) were male. One subject had Hb S-β^+ thalassemia and the other 26 had Hb SS or S-β^0 thalassemia. Figure 1 shows the children evaluated for inclusion and the number of MRI/MRAs reviewed.

Patient characteristics

Median age at initiation of chronic transfusion therapy was 6.83 years (interquartile range [IQR] 5.4–10.28). The indication for chronic transfusion therapy initiation was abnormal TCD in 3 (11%), overt stroke in 19 (70%), and SCI in 5 (18%) (Table I). Twenty-six of 27 patients included for analysis had cerebral infarcts documented at initiation of chronic transfusion therapy: 7 had overt stroke, 6 had silent stroke, and 13 had both overt and silent strokes. One child who started transfusion therapy due to an abnormal TCD and three children with overt strokes had their first MRI or MRA performed several months to years later; therefore, these four subjects' silent stroke burden and presence or severity of vasculopathy was unknown at transfusion therapy initiation. Chronic transfusion goals were to maintain Hb S <30% in all subjects for 2 years after starting transfusion therapy; subsequently the goal remained <30% in 21(78%) and was liberalized to <50% in 6 (22%). Subjects had a total of 263.1 patient-years of follow-up after initiation of transfusion therapy,

median 9.68 years (IQR 5.33–13.65). A total of 203 MRI/MRA reports were reviewed. Two subjects died during the follow-up period: a 20-year-old female who did not undergo cerebral revascularization surgery died of complications of a matched unrelated donor HSCT, and a 21-year-old male died of acute multisystem organ failure without further details available, approximately two years following cerebral revascularization.

Fourteen of 27 children (52%) had new or enlarging silent infarcts identified on MRI or recurrent overt strokes during the follow-up period (range 0–3 new infarcts per patient), yielding an overall silent plus overt infarct recurrence of 7.98 events/100 patient-years.

Cerebral vasculopathy was present at initiation of chronic transfusion therapy in 20 (74%) and was identified after initiation of chronic transfusion therapy in 3 (11%). Presence of cerebral vasculopathy at the time of transfusion therapy initiation was unknown in four subjects (15%), two of whom had initial MRIs performed at a referring institution (thus imaging studies were unavailable for review) and two of whom did not undergo MRA at initiation of chronic transfusion therapy. During the follow-up period, 23 (85%) of the children had progression of cerebral vasculopathy identified on clinical MRAs. Progression of vasculopathy was associated with new overt and silent infarcts (odds ratio 2.6, 95% CI 1.6, 4.3; Fisher's exact test p = 0.041).

Comparison of revascularization and no revascularization groups

Indirect cerebral revascularization surgery was performed in 12 of 27 children, at a median 4.03 years (IQR 1.87–7.04) following initiation of chronic transfusion therapy. The indications for revascularization surgery, as documented by subjects' treating physicians, were TIA, recurrent silent or overt stroke, progressive vasculopathy, educational problems/school failure, and/or headaches; 11 children had more than one of these signs of progressive cerebrovascular disease despite chronic transfusion therapy. (Table I). Compared with children who did not undergo cerebral revascularization, those in the revascularization group were younger at chronic transfusion therapy initiation (median 5.5 years, IQR 3.5–9.1, vs median 7.7 years, IQR 6.3–10.7, p=0.037) and were more likely to have TIAs (8/12 children, 66.7%, vs 3/15 children, 20%, p=0.02). There was no difference in sex, duration of follow-up after beginning transfusion therapy, presence of overt or silent strokes or cerebral vasculopathy at transfusion therapy initiation, headaches, or school failure between the groups (Table I). All 12 children in the revascularization group were prescribed aspirin, along with 3/15 (20%) of children who did not have revascularization (p<0.001).

Cerebral revascularization surgery and immediate postoperative outcomes

Eleven children underwent pial synangiosis (4 unilateral, 7 bilateral) and one child underwent bilateral burr hole placement with dural opening, for a total of 20 hemispheres treated. Six subjects with bilateral vasculopathy had staged pial synangiosis, with approximately one month separating the two hemispheres' surgeries, while one subject had pial synangiosis performed on both hemispheres on the same day. Two children experienced post-operative TIAs localizing to the operated cerebral hemisphere, both without new infarct lesions on MRI. No children had strokes in the immediate post-surgical period. One subject

developed a small subarachnoid blood collection post-operatively that caused fevers and headache; symptoms resolved with a short course of corticosteroids.

Three children incurred non-neurologic surgical complications. Two children developed a post-operative wound infection, both of which resolved with antibiotics, and one child had false tracking of a Foley catheter prior to surgery. None of the surgical complications resulted in permanent consequence to the affected patients.

Comparison of infarct recurrence between groups

Prior to cerebral revascularization, silent plus overt infarct recurrence in the revascularization group was 13.4 events/100 patient-years during 59.63 patient-years of follow-up (95% CI 5.79, 26.4), not significantly different from the silent plus overt infarct recurrence rate of 8.87 events/100 patient-years in the non-revascularization group during 146.45 patient-years of follow-up (95% CI 4.73, 15.2) (p=0.4). Following cerebral revascularization, the infarct recurrence rate in the revascularization group was 0 events/100 patient-years during 57.0 patient-years of follow-up. This was significantly lower than this group's pre-revascularization infarct recurrence rate (p=0.0057), and furthermore was significantly lower than the overall infarct recurrence rate in the non-revascularization group (p=0.025). Thus while the infarct recurrence rate was similar between groups at baseline, the children who underwent revascularization had a significant reduction in infarct recurrence post-revascularization compared with their own baseline and with the non-revascularization group (Figure 2).

Three of the eight children with history of TIAs had no additional TIAs following cerebral revascularization surgery; the remaining five children reported a decreased frequency and severity of TIA events. None of the 4 patients without pre-revascularization TIAs developed TIAs post-operatively.

Aside from the subarachnoid blood collection in a post-revascularization patient noted above, there were no other intracranial or other hemorrhages in 15 children receiving aspirin. One subject with moyamoya collaterals who neither took aspirin nor underwent cerebral revascularization therapy had a spontaneous intraventricular hemorrhage, causing acute hydrocephalus and a new SCI; he had prior overt strokes and progressive moyamoya despite chronic transfusion therapy.

HSCT and cerebral vasculopathy

Five children, all female, received HSCT during the study period: one matched sibling donor, three matched unrelated donor, and one haploidentical transplant. Two teens, neither of whom underwent cerebral revascularization, had new infarcts following HSCT: a 15-year-old had an overt stroke 2 months after HSCT and posterior reversible encephalopathy syndrome 8 months after HSCT resulting in hemiparesis and chronic infarcts on MRI, and a 19-year-old had stable infarcts on MRI 7 months after HSCT but progression of SCIs on MRI 15 months after HSCT. This latter subject subsequently died of multisystem organ failure 18 months after HSCT. A 10-year-old underwent matched unrelated donor HSCT 18 months after bilateral cerebral revascularization without any post-HSCT neurological complications. The recipients of matched sibling donor (age 7 years) and haploidentical (age

21 years) HSCT had no neurological complications following transplant; neither of them have undergone cerebral revascularization.

Figure 3 depicts the longitudinal course of each patient from transfusion therapy initiation to last follow-up, with silent and overt strokes, TIAs, revascularization surgery, and HSCT denoted.

Discussion

In this cohort study, both overt and silent stroke recurrence declined after cerebral revascularization surgery, providing further evidence that indirect cerebral revascularization is beneficial in children with SCD and moyamoya. Our report adds 12 cases of cerebral revascularization surgery in children with SCD, increasing the published total to 74 children, encompassing 118 cerebral hemispheres.[9,13,17–20] In all of these series, overt stroke recurrence is decreased following revascularization surgery. In addition, we provide the first indication that cerebral revascularization may reduce SCI recurrences in children receiving transfusion therapy.

This cohort of children with SCD and vasculopathy/moyamoya had an overall infarct recurrence rate on transfusion therapy of 7.98 infarcts/100 patient-years, comparable with a previously published cohort of children receiving chronic transfusion therapy for secondary stroke prevention.[7] The children in the revascularization surgery group had several features that may indicate more severe cerebrovascular disease, including younger age at initiation of chronic transfusion therapy and occurrence of TIAs, but their pre-revascularization infarct recurrence rate was similar to the children in the no revascularization group. The significantly lower infarct recurrence rate following indirect revascularization, despite the subjects' more severe preoperative features, suggests that children with SCD and severe cerebral vasculopathy/moyamoya but without TIAs or recurrent infarcts may derive similar benefit. Further, our data suggest that children may benefit more from this procedure before they have had multiple cerebral infarcts, since each infarct carries a risk of physical and cognitive morbidity.

While not clinically obvious, SCIs cause significant intellectual impairment among children with SCD. In the Silent Infarct Transfusion study, the presence of SCIs was associated with a 5-point decrease in intelligence quotient (IQ).[21] The severity of intellectual impairment worsens with increasing volume of cerebral infarction,[22] and children with overt strokes have even poorer cognition than those with SCIs alone.[23,24] Cognition in children with moyamoya due to SCD is more impaired than in subjects with non-SCD moyamoya, with lower baseline IQ and a further decline in IQ after a median follow-up of 3 years.[25] By extension, our data showing prevention of both SCIs and overt strokes following indirect revascularization suggest that revascularization may limit cognitive deterioration in children with SCD and moyamoya. Not surprisingly, more than half of our subjects had significant school difficulties or grade failure. However, due to the study's retrospective design, we could not compare cognitive outcomes in children in the revascularization and no revascularization groups.

The impact of TIAs on recurrent stroke risk and quality of life has not been quantified in children with SCD and moyamoya. The Cooperative Study of Sickle Cell Disease identified TIA as the strongest clinical risk factor for first stroke, with a relative risk of 56 for future first stroke.[2] In our study, subjects with TIAs were more likely to undergo cerebral revascularization surgery, potentially reflecting clinicians' and parents' concern that TIAs portend a more serious clinical event. All eight of the children in our study who had TIAs and underwent cerebral revascularization surgery had reduction or elimination of TIAs post-operatively, suggesting improvement in brain oxygen delivery; however, the continued TIAs in some of the children strongly suggest that they remain at risk of cerebral infarction.

This study is limited chiefly by its small sample size and retrospective design. Infarct recurrence risk may change over time, even in children with moyamoya. In this cohort, children were offered revascularization surgery at different timepoints after diagnosis of moyamoya, which may have limited our ability to discern differences in infarct recurrence rate between subjects who did and did not undergo revascularization. Our data set was limited by lack of Hb S concentrations in subjects in both groups. While common practice is to maintain Hb S concentrations below 30% on transfusion therapy, the optimal transfusion target has not been defined in prospective studies.[26] Furthermore, multiple cohort studies have identified progressive cerebral vasculopathy/moyamoya and infarctions in patients with SCD despite Hb S concentrations maintained below 30%[7,27,28] or even following successful HSCT.[29] These reports, plus the fact that moyamoya occurs in many patient populations without SCD, suggest that correction of Hb S is inadequate to prevent cerebral vasculopathy/moyamoya progression once this pathological cascade is initiated.[30] Finally, because aspirin treatment was significantly more common in children who underwent revascularization surgery, it is possible that the reduction in stroke recurrence rate is in part due to the effect of aspirin. However, this seems unlikely for several reasons. First, aspirin alone is not the standard treatment for children with idiopathic moyamoya or moyamoya due to other syndromes;[11] second, some centers have reported similar reductions in overt stroke recurrences following cerebral revascularization in SCD patients not prescribed aspirin,[9,20] suggesting that cerebral revascularization, and not aspirin, is the cause of improvement. Even with these limitations, our results corroborate prior publications indicating a significant reduction in both overt and silent stroke recurrence rate following revascularization.

There is no standard approach to management of progressive cerebral vasculopathy in children with SCD. HSCT, the only curative therapy for SCD, has been recommended as a treatment for cerebral vasculopathy by some[31] but is not available for all patients due to lack of matched sibling donors or adequately matched alternative donors. While successful HSCT provides long-term protection against overt strokes in most recipients, vasculopathy progression following HSCT has been reported in several cohorts,[29,32] suggesting that, once initiated, vasculopathy may progress independently of the presence of sickled red blood cells. Our data suggest that children may remain at risk of recurrent or progressive infarcts following HSCT if they have severe vasculopathy/moyamoya prior to HSCT, with two subjects in our study having new overt or silent infarcts post-HSCT. Whether pre-HSCT cerebral revascularization provides additional protection against neurological injury in

children undergoing HSCT is unknown and should be investigated in upcoming clinical studies.

Given the relative rarity of moyamoya in children with SCD, therapy options have not been studied prospectively. Cerebral revascularization is recommended for children with SCD and moyamoya at many centers based on its demonstrated benefit in children with idiopathic moyamoya or moyamoya due to other syndromes.[33] Pial synangiosis has been reported most frequently in children with SCD, but other surgical approaches include burr hole placement with dural opening, an indirect revascularization approach relying on ingrowth of new blood vessels, and direct anastomosis between the superficial temporal artery and middle cerebral artery, which immediately restores blood flow but is more technically difficult in children.[34] The small numbers of subjects in each of the published SCD cohorts indicate a need for prospective multicenter studies incorporating measures of cerebral function such as cognition and oxygen metabolism[35] as well as structural MRI/MRA and patient-reported outcomes. Such studies will improve understanding of the impact of treatments including cerebral revascularization, chronic transfusion therapy, and HSCT on TIAs, cerebral infarctions, and quality of life.

In conclusion, while multiple studies have shown that children with SCD and moyamoya have a significantly lower rate of overt stroke recurrence following cerebral revascularization surgery, this is the first to specifically describe protection from SCI recurrence. Prospective studies are needed to compare outcomes of cerebral revascularization with other treatment options for children with SCD and moyamoya.

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Abbreviations

SCD	Sickle cell disease
SCI	Silent cerebral infarction
Hb	Hemoglobin
MRI/MRA	Magnetic resonance imaging/magnetic resonance angiography
TIA	Transient ischemic attack
IQ	Intelligence quotient

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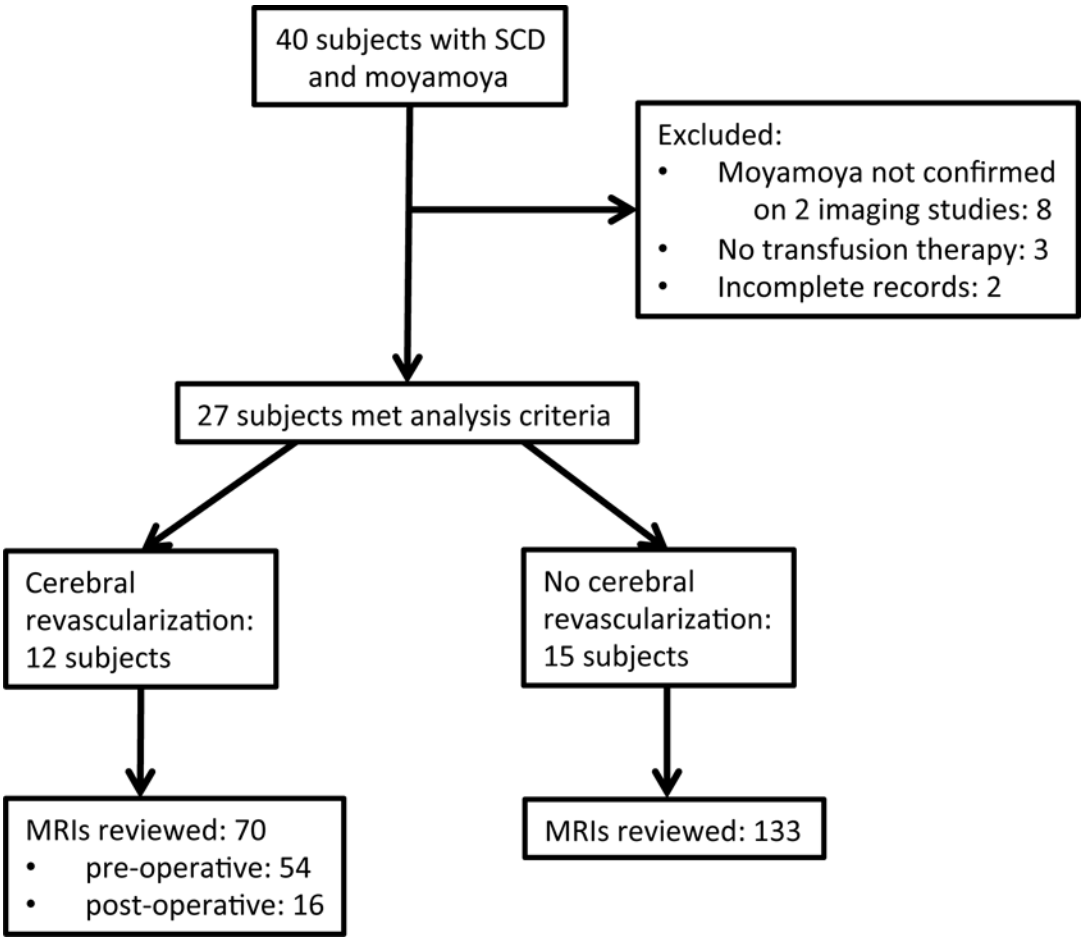

Figure 1.
Subjects Evaluated for Analysis

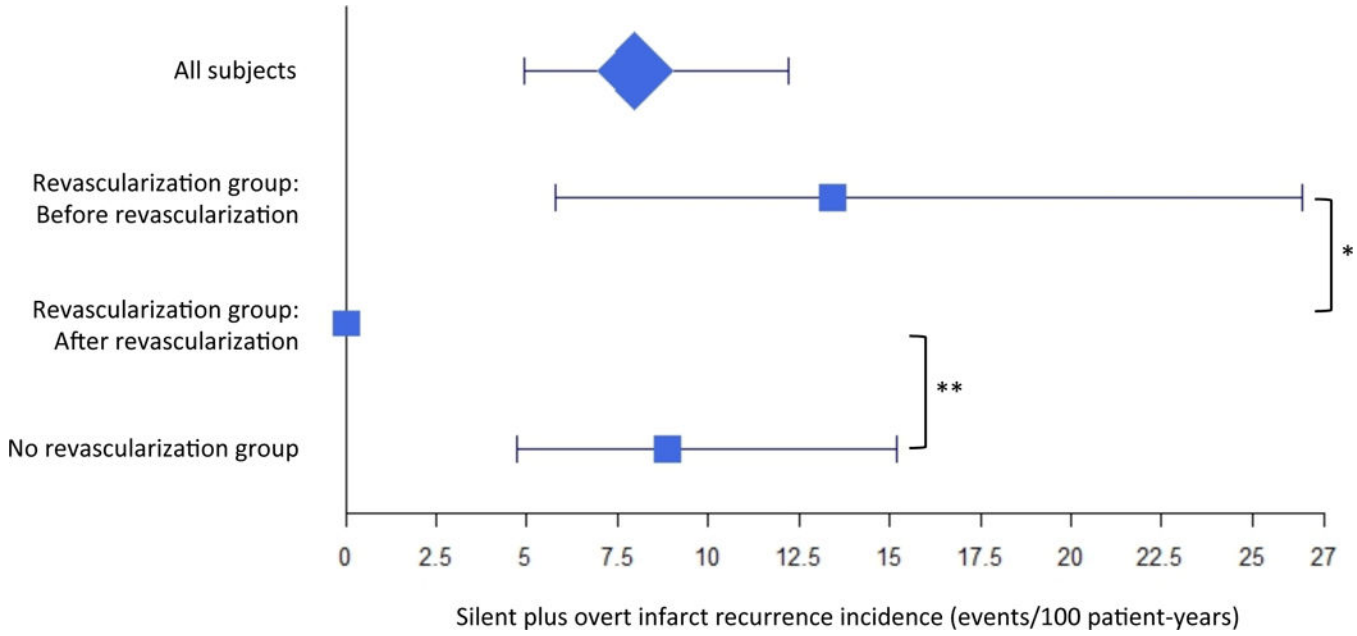

Figure 2.

Comparison of Silent plus Overt Infarct Recurrence Incidence while Receiving Chronic Transfusion Therapy. The 12 subjects who underwent cerebral revascularization surgery had a significant reduction in incidence of infarct recurrence compared to their own pre-revascularization baseline (*p=0.0057), and compared to the infarct recurrence incidence in the 15 subjects who did not undergo revascularization (**p=0.025).

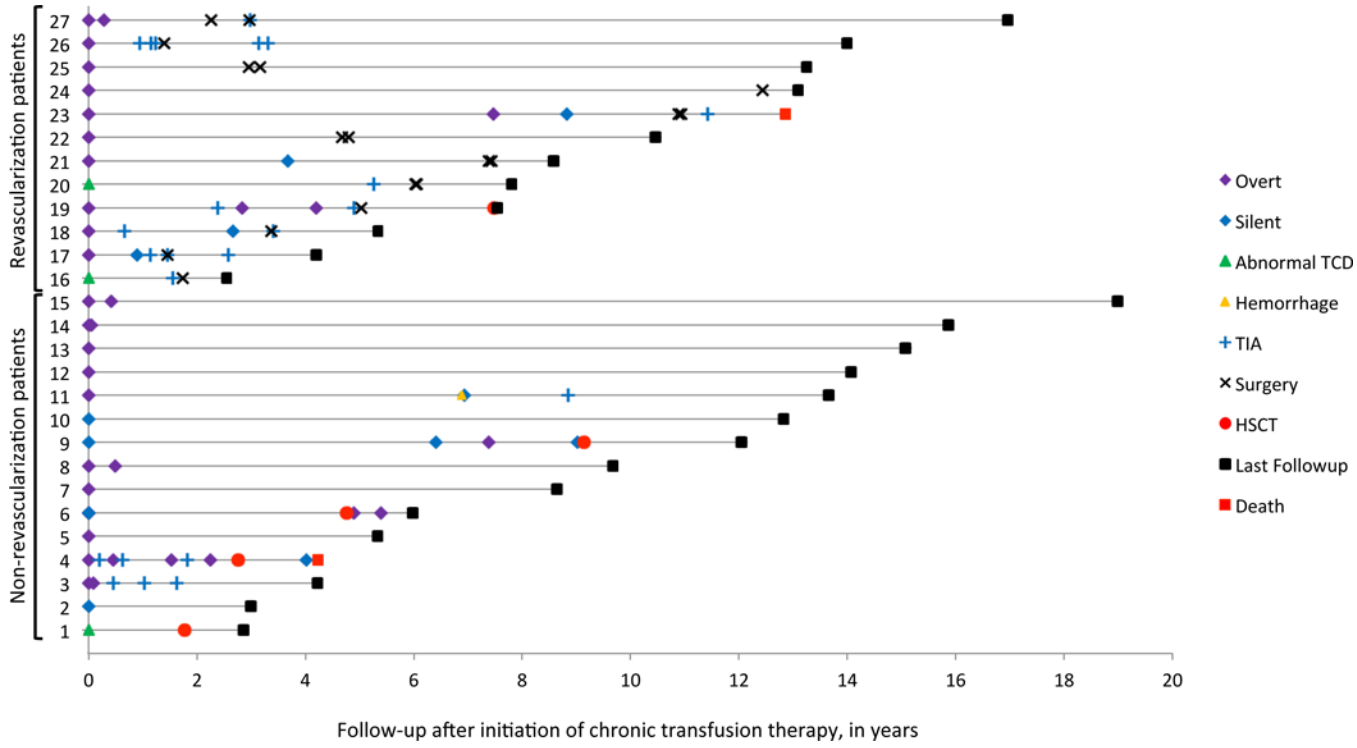

Figure 3.

Time Course of Infarct Recurrence, TIAs, and Revascularization Surgery Following Initiation of Chronic Transfusion Therapy for Stroke Prevention. Each horizontal line represents a single patient, with neurological events and treatments denoted. Patients 1–15 did not have revascularization surgery, while patients 16–27 had revascularization surgery. Patients 16, 17, 18, and 24 had unilateral revascularization, while the rest of the patients in the revascularization group had bilateral revascularization surgery.

Table I

Neuroimaging, Clinical Symptoms, and Treatments Prescribed for Children with Sickle Cell Disease and Severe Cerebral Vasculopathy

	Revascularization surgery (N=12)	No revascularization surgery (N=15)	P value
Sex (% male)	67	47	0.4
Median age at transfusion therapy initiation (y)	5.6	7.7	0.037 *
Median time followed after initiation of transfusion therapy (y)	9.5	9.7	0.9
Present at transfusion therapy initiation			
Cerebral infarction	11 (91.7%)	15 (100%)	0.4
Overt	10 (83.3%)	10 (66.7%)	0.4
Silent	8 (66.7%)	12 (80%)	0.7
Abnormal TCD	3 (25%)	1 (6.7%)	0.3
Vasculopathy	9 (75%)	10 (66.7%)	0.7
Neurological symptoms or signs after transfusion therapy initiation			
New infarct	6 (50%)	8 (53.3%)	1
New overt	3 (25%)	7 (46.7%)	0.4
New silent	4 (33.3%)	3 (20%)	0.7
TIA	8 (66.7%)	3 (20%)	0.02 **
Vasculopathy progression	10 (83.3%)	13 (86.7%)	1
Headaches	5 (41.7%)	5 (33.3%)	0.7
Educational problems or grade failure	8 (66.7%)	9 (60%)	1
Other treatments			
Aspirin	12 (100%)	3 (20%)	<0.001 **
HSCT	1 (8.3%)	4 (26.7%)	0.3

TCD = transcranial Doppler ultrasound, TIA = transient ischemic attack, HSCT = hematopoietic stem cell transplant.

* Independent-samples Mann-Whitney U test,

** Fisher's exact test.