Is Smoke the Signal for Surgery? : Should the Moyamoya Syndrome "Puff of Smoke" trigger cerebral revascularization surgery in children with sickle cell disease?

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Abstract

Stroke in Sickle Cell Revascularization Surgery Retrospective Study (SiSCRS) in this issue reports retrospective data from 15 medical centers to examine the benefit of cerebral revascularization surgery (CRS) in children with sickle cell disease (SCD) who also have Moyamoya Syndrome (SCD-MMS). The American Society of Hematology guidelines "suggests evaluation for revascularization surgery in addition to regular blood transfusion" for treating SCD-MMS combined with a history of stroke or transient ischemic attack but categorizes this as a "conditional recommendation based on very low certainty in the evidence about effects". The research presented in this article is aimed at reducing the uncertainty surrounding revascularization surgery as a treatment using retrospective data from 15 medical centers with expertise in CRS for SCD-MMS. Even with the 78 children with CRS (Surgery group) and 63 children in the non-surgery (Conservative group), the differences between the two groups had mixed statistical significance in multivariate analyses. SiSCRS is an important retrospective analysis but must be interpreted with caution. The benefit of CRS attains statistical significance only in some of the comparisons. The rate of stroke in pediatric SCD decreases with age, creating a bias in favor of the older group (i.e., the Surgery Group) to have fewer CVEs, The additional role of aspirin and the bias of patient selection for surgery also weaken the ability to make definitive statements. The SiSCRS results suggest a likely retrospective benefit of CRS, but the benefit must be demonstrated with more rigorous studies in the future.

Smoke Signal for Surgery?

Should the Moyamoya Syndrome "Puff of Smoke" trigger cerebral revascularization surgery in children with sickle cell disease?

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Abbreviations

CRS	Cerebral revascularization surgery
CVE	Cerebrovascular events: stroke or transient ischemic attack
MRI	Magnetic resonance imaging of the brain
SCD	Sickle cell disease
SCD-MMS	Sickle cell disease with moya-moya syndrome
SiSCRS	*Stroke in Sickle Cell Revascularization Surgery Retrospective Study*

This is an invited editorial commentary on: *PBC-22-1057 - Cerebral Revascularization Surgery Reduces Cerebrovascular Events in Children with Sickle Cell Disease and Moyamoya Syndrome Results of the Stroke in Sickle Cell Revascularization Surgery (SiSCRS) Retrospective Study*

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ABSTRACT

Stroke in Sickle Cell Revascularization Surgery Retrospective Study (SiSCRS) in this issue reports retrospective data from 15 medical centers to examine the benefit of cerebral revascularization surgery (CRS) in children with sickle cell disease (SCD) who also have Moyamoya Syndrome (SCD-MMS). The American Society of Hematology guidelines "suggests evaluation for revascularization surgery in addition to regular blood transfusion" for treating SCD-MMS combined with a history of stroke or transient ischemic attack but categorizes this as a "conditional recommendation based on very low certainty in the evidence about effects". The research presented in this article is aimed at reducing the uncertainty surrounding revascularization surgery as a treatment using retrospective data from 15 medical centers with expertise in CRS for SCD-MMS. Even with the 78 children with CRS (Surgery group) and 63 children in the non-surgery (Conservative group), the differences between the two groups had mixed statistical significance in multivariate analyses. SiSCRS is an important retrospective analysis but must be interpreted with caution. The benefit of CRS attains statistical significance only in some of the comparisons. The rate of stroke in pediatric SCD decreases with age, creating a bias in favor of the older group (i.e., the Surgery Group) to have fewer CVEs, The additional role of aspirin and the bias of patient selection for surgery also weaken the ability to make definitive statements. The SiSCRS results suggest a likely retrospective benefit of CRS, but the benefit must be demonstrated with more rigorous studies in the future.

Highlight:

Is Smoke the Signal for Surgery?

Should the Moyamoya Syndrome "Puff of Smoke" trigger cerebral revascularization surgery in children with sickle cell disease?

The moya-moya syndrome describes a tangled cloud of small fragile collateral blood vessels, resulting from the ischemic brain's desperate release of vascular growth signals when it does not receive adequate blood flow. In this issue of Pediatric Blood and Cancer, the*Stroke in Sickle Cell Revascularization Surgery Retrospective Study* (SiSCRS) [1] reports retrospective data from 15 medical centers to examine the benefit of cerebral revascularization surgery (CRS) in children with sickle cell disease (SCD) who also have Moyamoya Syndrome (SCD-MMS). Ischemic stroke is one of the most devastating complications of SCD, leading to motor, sensory, and cognitive deficits. Ischemia can also lead to "silent cerebral infarcts" detected only by magnetic resonance

imaging of the brain (MRI). In sickle cell anemia without any intervention, the incidence of stroke can be 20% and the incidence of silent cerebral infarct is as high as 39% [2].

Therapeutic progress has greatly reduced the cerebrovascular complications of SCD. Transcranial doppler ultrasound screens for high-risk patterns of blood flow [3], and MRI screens for silent cerebral infarcts. Strategies to improve oxygen transport to the brain include correcting anemia, diluting sickle erythrocytes, and reducing hemolysis. Both chronic transfusions and hydroxyurea are used to reduce stroke risk, and hematopoietic stem cell transplant can halt sickle cell pathophysiology [2].

However, therapies are less effective in reducing the risk of ischemic stroke for the subset of SCD with the most severe cerebrovascular abnormalities: SCD-MMS. Current American Society of Hematology guidelines "suggests evaluation for revascularization surgery in addition to regular blood transfusion" for treating SCD-MMS combined with a history of stroke or transient ischemic attack but categorizes this as a "conditional recommendation based on very low certainty in the evidence about effects" [2]. The SiSCRS group aimed to reduce the uncertainty surrounding revascularization surgery as a treatment using retrospective data from 15 medical centers with expertise in CRS for SCD-MMS.

SiSCRS comparison of Surgery and Conventional treatment indicate moderate support (OR=0.27) that CRS is associated with the post-surgical reduction of cerebrovascular events (CVEs). As further evidence of the benefit of CRS, the authors present the result that significantly fewer CVEs were found post-treatment in the Surgery group compared to pre-surgery. However, "there were no statistically significant differences when comparing rates of designated ischemic events (ischemic strokes or TIAs) by group (Table 2)."

A major strength of the study is that 15 centers pooled a larger retrospective sample of SCD-MMS than previous single-institution studies [1]. However, even with the 78 children with CRS (Surgery group) and 63 children in the non-surgery (Conservative group), the differences between the two groups had mixed statistical significance in multivariate analyses. This was especially notable for those with a history of prior cerebrovascular events (CVEs).

The analyses carefully considered age and length of risk period as potential confounders but, as in any retrospective analysis, potential unmeasured confounders could not be accounted for. The sample size per medical center made it impossible to determine site effects.

Indications for CRS were not described, but referral to CRS could be triggered when a stroke occurs despite chronic transfusion therapy [4]. However, at least two lines of evidence suggest that, if the CRS was done at the time that recurrences would diminish anyway, then the benefit of CRS could be confounded with the benefit of time.

(1) Stroke rates in non-transfused SCD children decline with age, notably between the 6-9yo compared to the 10-19yo range [5]. The "age of treatment start" was 11.0 + 4.7 for the Surgery group and 6.8 + 4.0 for the Conservative Group. The graphs showing the decreased rate of CVEs with age in Figures S15- S18 resemble some of the data from natural history. Statistical models used in the article show an inverse correlation between age and logit-transformed data for CVEs, but the scatter of the data is very large.

(2) The highest stroke recurrence rates were in the first 3 years after the initial stroke for non-transfused children [6].

Additional potential confounders could be hidden by major changes in the national standard of care that were introduced during the period of data collection from 1990 to 2017: screening using transcranial doppler examination [3], hydroxyurea for pediatric SCD [7], and heterogeneous adoption of other interventions like automated erythrocytapheresis for stroke prevention [8]. Aspirin was used more widely in the Surgery group than the Conservative group, so that the protective effect of aspirin against CVE might be another confounding variable.

The adverse events reported within 30 days of surgery included 2 ischemic strokes and 2 TIAs among the 78 children with CRS. There were no perioperative deaths and no permanent neurologic sequelae, indicating a

low risk compared to other neurosurgical procedures.

SiSCRS should be praised for providing a solid foundation for a larger multicenter controlled study. Their data estimate effect size and present sample sizes to make power calculations possible. They identify confounders like age, follow-up duration, prior CVE, and aspirin usage; a future study might need to design stratification by age. They highlight that future multivariate analysis could examine the role of CVE type and the time-dependent relationship between CVE history and subsequent CVE occurrence. Whether randomized assignment to CRS vs no CRS has equipoise is not clear. Asymptomatic MR screening for silent infarcts might provide a cohort with early detection of SCD-MMS. Functional data with Modified Rankin Scale could be collected across all patients.

Thus, SiSCRS is an important retrospective analysis that suggests a likely retrospective benefit of CRS for SCD-MMS, but must be interpreted with caution. The benefit of CRS attains statistical significance only in some of the comparisons. The rate of stroke in pediatric SCD decreases with age, creating a bias in favor of the older group (i.e., the Surgery Group) to have fewer CVEs. Which children with SCD-MMS benefit from CRS, and when to refer, must be demonstrated with future studies that build upon the foundation provided by SiSCRS data.

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