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Narrative Review

Hydroxyurea for the Prevention of Stroke in Sick Cell Anaemia: Mechanisms, Clinical Trial Evidence, and Global Implementation

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Abstract:

Background: Stroke is among the most serious complications of sickle cell anemia (SCA), affecting a substantial proportion of children and historically carrying a recurrence risk exceeding 50% after a first overt event. Transcranial Doppler (TCD) screening followed by chronic red-cell transfusion reduces first-stroke risk by more than 90%, but transfusion must be continued indefinitely and is constrained by iron overload, all immunization, venous access, and, most critically, limited feasibility in the low- and middle-income countries where the majority of affected children live.

Mechanisms: Hydroxyurea, the first disease-modifying therapy for SCA, is an oral, inexpensive agent. By inducing fetal hemoglobin and exerting pleiotropic effects on erythrocyte hydration, leukocyte and reticulocyte counts, cellular adhesion, inflammation, and nitric oxide-dependent vascular tone, it reduces HbS polymerization, sickling, and vaso-occlusion, thereby lowering cerebral arterial flow velocities.

Clinical evidence: This review synthesizes the mechanistic rationale and randomized-trial evidence for hydroxyurea in stroke prevention, distinguishing primary from secondary prevention. For primary prevention, the TWiTC trial established non-inferiority of hydroxyurea to transfusion for maintaining TCD velocities, and trials in sub-Saharan Africa (SPIN, SPHERE, SPRING) confirmed effectiveness even at low fixed doses. For secondary prevention, chronic transfusion remains standard where available; the SPRINT trial and observational data support hydroxyurea as an alternative when transfusion is not feasible. The REACH trial additionally linked hydroxyurea to a significant reduction in all-cause mortality.

Conclusions: Hydroxyurea has a favorable safety profile, and because recently approved gene therapies exclude patients with cerebrovascular disease and remain globally inaccessible, it is the practical foundation of stroke prevention in SCA worldwide. Questions about optimal dosing, treatment duration, and long-term neurocognitive outcomes warrant continued investigation.

Keywords: sickle cell anemia; hydroxyurea; stroke prevention; fetal hemoglobin; transcranial Doppler; vaso-occlusion

1. Introduction

Sickle cell anemia (SCA) is an inherited disorder caused by a single point mutation in the β -globin gene (HBB) and transmitted in an autosomal recessive manner.^{1,2} The mutation substitutes valine for glutamic acid at position 6 of the β -globin chain; upon deoxygenation, the resulting sickle hemoglobin (HbS) polymerises into rigid fibres that deform erythrocytes, promote hemolysis, and obstruct the microcirculation,

initiating a self-amplifying cycle of vaso-occlusion, inflammation, and endothelial injury that underlies both acute crises and chronic organ damage.^{3,4}

SCA imposes a substantial and rising global burden: more than 500,000 affected births occur each year, the great majority in sub-Saharan Africa, and several million people live with the disease worldwide.⁵⁻⁷ Stroke is among the most devastating of its complications, particularly in childhood.^{8,9} Hydroxyurea, the first disease-modifying therapy approved for SCA, reduces vaso-occlusive crises, acute chest syndrome, transfusion requirements, and hospitalisations, and has become foundational to comprehensive care.³

This review synthesises the mechanistic rationale and randomised-trial evidence for hydroxyurea in stroke prevention in SCA, distinguishing primary from secondary prevention and emphasising implementation in the resource-limited settings where most affected children live.

2. Burden and Pathophysiology of Cerebrovascular Disease in Sickle Cell Anaemia

Cerebrovascular disease in SCA spans a spectrum from silent cerebral infarction, which is detected in a sizeable proportion of children and accumulates with age, to overt ischemic stroke, which characteristically reflects large-vessel arteriopathy of the distal internal carotid and proximal middle cerebral arteries.¹⁰ Before screening and prophylaxis became routine, a first overt stroke carried a recurrence risk greater than 50% within several years.^{9, 10}

Ischemic stroke in SCA arises from the same vaso-occlusive process that affects the systemic circulation. Under hypoxic conditions, reduced oxygen affinity and elevated 2,3-diphosphoglycerate favour HbS polymerisation,¹¹ which stiffens erythrocytes, promotes hemolysis, and occludes small vessels.¹² Hemolysis releases cell-free haemoglobin and heme; once the scavenging capacity of haptoglobin, hemopexin, and nitric oxide is exhausted, free haemoglobin and heme accumulate and drive oxidative stress, endothelial damage, and inflammation.¹³⁻¹⁶ Heme generates reactive oxygen species that provoke sterile inflammation and activate platelets, neutrophils, reticulocytes, and endothelial cells.¹⁷ This injury is compounded by reduced superoxide dismutase 2 expression in SCA, which further impairs antioxidant defense.^{18,19} Increased erythrocyte rigidity and blood viscosity, together with upregulated adhesion molecules such as P-selectin, anchor sickle erythrocytes and leukocytes to the endothelium and perpetuate microvascular obstruction.²⁰⁻²² Recurrent vaso-occlusion produces cyclical ischemia and reperfusion injury, endothelial dysfunction, and a progressive vasculopathy.²³

3. Conventional Prevention and Its Limitations

Transcranial Doppler ultrasonography identifies children at high risk of a first stroke. In the landmark STOP trial, children with abnormal TCD velocities (≥ 200 cm/s) who received chronic transfusion to maintain HbS below 30% had their first-stroke risk reduced by more than 90%, and the trial was stopped early for efficacy.²⁴ However, the subsequent STOP 2 trial showed that discontinuing transfusion led to rapid reversion to abnormal velocities and to stroke, indicating that protective transfusion must be continued indefinitely.²⁵

Although effective, chronic transfusion imposes considerable long-term burdens, including transfusional iron overload requiring chelation, all immunization, transfusion-transmitted infection, and the logistical demands of repeated venous access and frequent hospital visits.^{26,27} Critically, chronic transfusion and its supporting infrastructure are largely unavailable in low- and middle-income countries, especially in sub-Saharan Africa, where most children with SCA live.²⁸ This gap created an urgent need for an effective, oral, and affordable alternative and motivated the investigation of hydroxyurea for stroke prevention.

4. Mechanisms of Action of Hydroxyurea

Hydroxyurea is an oral ribonucleotide reductase inhibitor with several mechanisms relevant to SCA. Its principal action is induction of fetal haemoglobin (HbF), which raises the intracellular threshold for HbS polymerisation and sickling.^{29, 30} HbF induction is mediated in part through a nitric oxide-soluble guanylyl cyclase-cyclic GMP signaling pathway that activates γ -globin expression.³¹

Beyond HbF, hydroxyurea improves erythrocyte hydration, lowers neutrophil and reticulocyte counts, and reduces pro-inflammatory mediators that drive vaso-occlusion. It downregulates adhesion molecule expression on erythrocytes, leukocytes, and endothelial cells, thereby improving microvascular flow and attenuating the cell-cell interactions that precipitate vaso-occlusive crises.³²⁻³⁴ Hydroxyurea also acts as a nitric oxide donor; because nitric oxide is a potent vasodilator and regulator of vascular tone, this property is thought to contribute to improved cerebral and systemic perfusion alongside its anti-adhesive effects.^{35,36} These mechanisms are summarised in Figure 1.

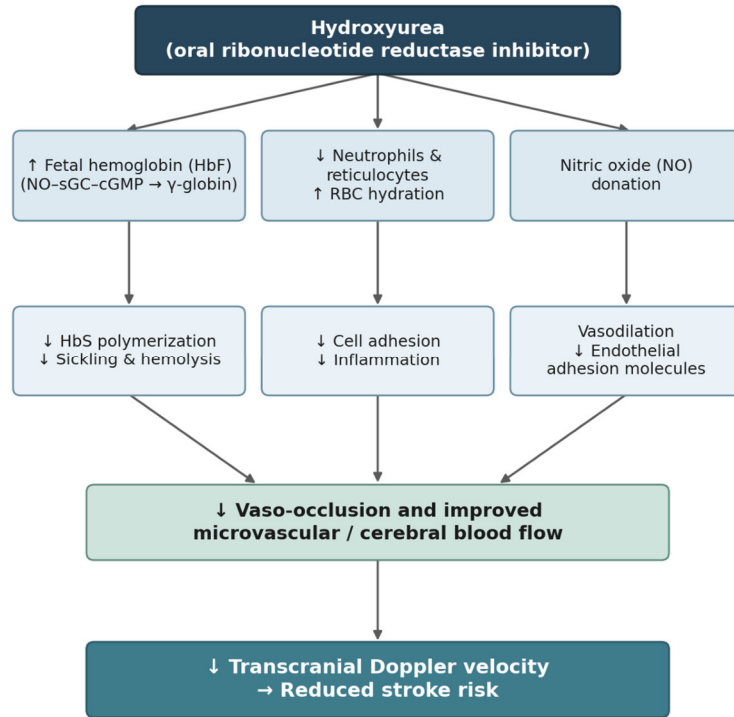


Figure 1. Principal mechanisms of hydroxyurea in sickle cell anemia. Hydroxyurea induces fetal hemoglobin (HbF) via a nitric oxide (NO)–soluble guanylyl cyclase (sGC)–cyclic GMP pathway, reduces neutrophil and reticulocyte counts while improving erythrocyte hydration, and donates NO. These actions reduce HbS polymerization and sickling, cellular adhesion and inflammation, and endothelial adhesion-molecule expression while promoting vasodilation, converging on reduced vaso-occlusion, improved cerebral blood flow, lower transcranial Doppler (TCD) velocity, and reduced stroke risk.

5. Clinical Evidence: Primary Stroke Prevention

The Twitch trial provided the pivotal evidence that hydroxyurea can replace transfusion for primary stroke prevention. In this phase 3, open-label, non-inferiority study conducted in the United States and Canada, children aged 4–16 years with abnormal TCD velocities but without severe vasculopathy, who had received at least one year of transfusion, were randomised to continue transfusion or to switch to hydroxyurea at the maximum tolerated dose with phlebotomy for iron management. Hydroxyurea was non-inferior, and potentially superior, to transfusion for maintaining 24-month TCD velocities while achieving better control of iron overload, and the trial was stopped early at the first interim analysis.³⁷ On this basis, the 2020 American Society of Haematology guidelines endorse hydroxyurea at the maximum tolerated dose for children with abnormal TCD who have already been stabilised on transfusion.³⁸

A parallel body of work has tested primary prevention directly in resource-limited settings. The SPIN feasibility trial in Nigeria showed that moderate fixed-dose hydroxyurea (approximately 20 mg/kg/day) could be safely delivered to children with abnormal TCD, achieving a stroke rate comparable to the transfusion-based STOP benchmark and superior to no treatment.³⁹ The open-label, phase 2 SPHERE trial in Tanzania combined TCD screening with hydroxyurea escalated to the maximum tolerated dose, producing a mean reduction in TCD velocity of approximately 35 cm/s, reversion to normal velocities in 83% of children, and no strokes during follow-up.⁴⁰ The phase 3 SPRING trial then randomized children aged 5–12 years with abnormal TCD to low-dose (10 mg/kg/day) or moderate-dose (20 mg/kg/day) hydroxyurea and found no difference in stroke incidence between groups, although moderate dosing may reduce all-cause hospitalization; these findings support low fixed-dose therapy where monitoring capacity is limited.⁴¹

Although designed to assess organ function rather than stroke, the BABY HUG trial demonstrated that hydroxyurea is safe and clinically beneficial from infancy, supporting early initiation,^{42, 43} and longitudinal neuroimaging studies have associated hydroxyurea with favorable brain MRI and MRA findings in children with SCA.⁴⁴

6. Clinical Evidence: Secondary Stroke Prevention

Secondary prevention after an overt stroke is more complex. The Switch trial compared hydroxyurea plus phlebotomy with transfusion plus chelation in children who had already had a stroke and had iron overload. It was halted early because recurrent strokes occurred in 7 of 67 children receiving hydroxyurea versus none of 66 receiving transfusion, and iron control was not superior; hydroxyurea therefore did not meet the criterion for non-inferiority, and chronic transfusion remains the standard of care where it is feasible.⁴⁵

However, when transfusion is not available, hydroxyurea is a reasonable alternative. The SPRINT trial in Nigeria randomised 101 children to low-dose or moderate-dose hydroxyurea within 30 days of stroke and found comparable recurrence rates between the two regimens, with no child discontinuing therapy for myelosuppression, indicating that low-dose hydroxyurea is sufficient for secondary prevention in settings without reliable transfusion access and reduces the need for frequent blood count monitoring.⁴⁶ Earlier case series likewise reported that higher-dose hydroxyurea begun after a first stroke was well tolerated and appeared to reduce recurrence while avoiding the complications of long-term transfusion.⁴⁷ Taken together, hydroxyurea offers meaningful protection for children who cannot access ongoing transfusion, even though it does not match the efficacy of transfusion in direct comparison.

7. Broader Clinical Benefit and Effect on Mortality

The benefits of hydroxyurea extend beyond stroke prevention. The REACH trial, conducted across four sub-Saharan African countries in children aged 1–10 years, showed that hydroxyurea escalated to the maximum tolerated dose reduced vaso-occlusive events, infections, malaria, and transfusion requirements and, most strikingly, produced a significant reduction in all-cause mortality.⁴⁸ Given the close links among infection, vaso-occlusion, and survival in this population, this broad benefit supports the wide use of hydroxyurea as part of comprehensive SCA care.

8. Safety, Tolerability, and Dosing

Hydroxyurea has been well tolerated across pediatric studies, with adverse effects that are typically mild and limited to transient cytopenias, occasional headache, and mild gastrointestinal symptoms; in BABY HUG, moderate fixed-dose therapy was not associated with excess severe neutropenia or thrombocytopenia.⁴² Dedicated safety cohorts, including the HUG-KIDS study and other pediatric and long-term series, have confirmed low rates of severe toxicity,⁴⁹⁻⁵² and the HUSOFT pilot study showed that liquid hydroxyurea was tolerated in infants with accompanying laboratory and clinical improvement.⁵³

A central practical question is the choice of dosing strategy. Escalation to the maximum tolerated dose maximizes HbF induction but requires careful titration and laboratory monitoring, whereas a fixed low-dose approach (10 mg/kg/day) is simpler and more scalable and provides comparable stroke prevention with a reduced monitoring burden.^{41, 46} The optimal strategy is therefore context-dependent: maximum tolerated dosing is appropriate where monitoring infrastructure exists, while fixed low-dose therapy is more practical where resources are constrained.

9. Place in Therapy and Future Directions

The recently approved cell-based gene therapies for SCA, including a CRISPR-based therapy and a lentiviral gene-addition therapy, represent a major advance.^{54,55} They are not, however, options for stroke prevention: they are indicated for patients 12 years and older with recurrent vaso-occlusive events, their pivotal trials excluded patients with prior stroke or abnormal TCD, and the requirement for myeloablative conditioning, specialized centers, and a cost of several million dollars per patient renders them inaccessible to the populations most affected by SCA-related stroke worldwide.⁵⁵ For the foreseeable future, hydroxyurea remains the practical foundation of stroke prevention because it is oral, affordable, and deliverable in primary care.³

Important questions remain. These include the optimal dose (maximum tolerated versus fixed low dose), the appropriate duration of therapy, whether and when children can be transitioned from transfusion to hydroxyurea, the value of biomarkers to guide therapy, long-term neurocognitive outcomes, and how hydroxyurea should be integrated with emerging curative approaches as access expands.

10. Conclusion

Hydroxyurea has emerged as a safe, effective, and globally implementable therapy for stroke prevention in sickle cell anemia. Through fetal hemoglobin induction, improved erythrocyte hydration, reduced cellular adhesion and inflammation, and nitric oxide-mediated vasodilation, it lowers transcranial Doppler velocities and reduces the risk of stroke. Randomized trials, including Twitch, SPIN, SPHERE, and SPRING, establish

hydroxyurea as an alternative to transfusion for primary prevention, effective even at low fixed doses, while chronic transfusion remains the standard for secondary prevention where it is available. With a favorable safety profile and benefits that extend to overall survival, and given that newly approved gene therapies remain inaccessible and unsuited to patients with cerebrovascular disease, hydroxyurea is the cornerstone of stroke prevention in SCA. Continued research and careful hematologic monitoring are needed to refine dosing, duration, and long-term outcomes.

Table 1: Key randomized trials and studies of hydroxyurea for stroke prevention and broader benefit in sickle cell anemia.

Trial / study	Design and population	Hydroxyurea regimen	Principal finding
<i>Primary stroke prevention</i>			
TWiTCH³⁷	Phase 3 non-inferiority (USA/Canada); children 4–16 y with abnormal TCD, ≥12 mo prior transfusion, no severe vasculopathy	Switch from transfusion to HU at MTD; phlebotomy for iron	HU non-inferior (potentially superior) to transfusion for 24-mo TCD velocity, with better iron control; stopped early
SPIN³⁹	Feasibility trial (Nigeria); children 2–16 y with abnormal TCD	Moderate fixed dose, ~20 mg/kg/day	Stroke rate comparable to transfusion (STOP benchmark) and superior to no treatment
SPHERE⁴⁰	Open-label phase 2 (Tanzania); children 2–16 y, conditional or abnormal TCD	HU escalated to MTD	Mean TCD velocity reduced ~35 cm/s; 83% reverted to normal; no strokes
SPRING⁴¹	Double-blind phase 3 (Nigeria); children 5–12 y with abnormal TCD	Low (10) vs moderate (20 mg/kg/day)	No difference in stroke between doses; moderate dose may reduce all-cause hospitalization
<i>Secondary stroke prevention</i>			
SWITCH⁴⁵	Phase 3 non-inferiority (USA); children with prior overt stroke and iron overload	HU + phlebotomy vs transfusion + chelation	Stopped early; recurrent stroke 7/67 (HU) vs 0/66 (transfusion); iron control not superior—transfusion preferred
SPRINT⁴⁶	Double-blind phase 3 (Nigeria); 101 children 1–16 y within 30 d of stroke	Low (10) vs moderate (20 mg/kg/day)	Comparable recurrence between doses; none stopped for myelosuppression; low dose sufficient where transfusion unavailable
Sumoza et al.⁴⁷	Case series; children with prior stroke	HU 30–40 mg/kg/day	Well tolerated with no major toxicity; apparent protection against recurrence
<i>Broader clinical benefit</i>			
REACH⁴⁸	Prospective open-label (4 sub-Saharan countries); children 1–10 y	HU escalated to MTD	Reduced vaso-occlusive events, infections, malaria, and transfusions; significant reduction in all-cause mortality

HU, hydroxyurea; MTD, maximum tolerated dose; TCD, transcranial Doppler.

Declarations

Funding. Nil

Conflicts of interest. Nil

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