Moderate-Dose Hydroxyurea for Primary Prevention of Strokes in Nigerian Children with Sickle Cell Disease: Final Results of the SPIN Trial

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In children with sickle cell anemia (SCA) living in high-income settings, the routine use of transcranial Doppler (TCD) measurements, coupled with monthly blood transfusion therapy for children with abnormal velocities (> 200 cm/sec, non-imaging), resulted in a 92% relative risk reduction in strokes when compared to no treatment.[1] More recently, the TWITCH Trial demonstrated that children with abnormal TCD measurements and no evidence of magnetic resonance angiography-defined cerebral vasculopathy, after one year of initial regular blood transfusion therapy, could be transitioned to hydroxyurea therapy at the maximum tolerated dose.[2] However, initial regular blood transfusion therapy for primary stroke prevention is not feasible for the vast majority of the children with SCA living in low- and middle-income settings.[3] Further, limited data are available to determine whether initial treatment with hydroxyurea rather than blood transfusion therapy is a durable therapy for primary stroke prevention.

To address this gap in knowledge for preventing strokes in children with SCA living in Africa, we tested the hypothesis that moderate fixed-dose hydroxyurea (~20 mg/kg/day) for primary stroke prevention was feasible in a low-income setting,
Kano, Nigeria. We previously demonstrated in the Stroke Prevention in Nigeria (SPIN) Trial (NCT01801423) that hydroxyurea was acceptable and safe for children with SCA and abnormal TCD measurements.[4] We have extended the feasibility trial for approximately five years to test the hypotheses that moderate fixed-dose hydroxyurea will: 1) not result in an excess incidence rate of serious adverse events (death or stroke) when compared to a group of children with SCA and TCD measurements < 200 cm/sec not receiving hydroxyurea; 2) comparable stroke incidence rate in children with abnormal TCD measurements initially and only treated with moderate dose hydroxyurea to those with abnormal TCD measurements in the STOP Trial initially and only treated with regular blood transfusion therapy.[1] We report the final results of the SPIN Trial.

At trial entry, eligible participants were screened with TCD, non-imaging technique, to determine increased stroke risk, defined as two independent measurements of time-averaged mean maximum velocity (TAMMV) ≥ 200 cm/sec or one measurement ≥ 220 cm/sec in the middle cerebral artery (MCA). Families of children with abnormal TCDs were offered regular blood transfusion therapy as standard care. If families refused regular blood transfusion, moderate fixed-dose hydroxyurea (~20 mg/kg/day) was offered via the SPIN trial; children were evaluated monthly with surveillance complete blood counts (CBCs). To primarily
address whether hydroxyurea was associated with an increased incidence of death when compared to children with SCA in the same age group not treated with hydroxyurea, we included a comparison group of children with SCA who were screened and had a TCD measurement of < 200 cm/sec, and agreed to be followed as part of routine care. Malaria prophylaxis and penicillin prophylaxis were prescribed to all participants as standard care. Serious adverse events including death or stroke, based on the World Health Organization criteria,[5] in the treatment and comparison groups, were recorded and compared.

Twenty-nine children with abnormal TCD measurements were identified and treated with moderate-dose hydroxyurea for primary stroke prevention, and 206 children were included in the comparison group. No caregiver of a child with abnormal TCD measurements elected to have their child treated with regular blood transfusion therapy. Among the comparison group, standard care TCD screening was performed on average every 12 months, and 4 children developed abnormal TCD measurements and crossed over to the treatment group. Baseline features and clinical outcomes of the treatment and comparison groups are shown in Table 1.

The median time on hydroxyurea therapy (follow-up time) was 4.8 years (IQR: 3.7, 5.6). The stroke incidence rate among participants on hydroxyurea was 0.76 per
100 person-years (95% CI: 0.11 – 5.24), which was not significantly different from
the much lower stroke risk participants in the comparison group who did not have
an elevated TCD velocity, incidence rate 0.43 per 100 person-years (95% CI: 0.16
– 1.15) (P = 0.603). Importantly, the incidence rate of strokes was significantly
lower than the stroke incidence rate reported in the standard care group for the
STOP trial (10.7 per 100 person-years, with a total of 102 person-years) where all
children had abnormal TCD velocity.[1] The stroke incidence rate was also similar
to the stroke incidence rate in the STOP trial transfusion group (0.9 per 100 person-
years with a total of 110 patient-years). In 29 participants monitored with monthly
CBCs (n=1560), no participant had hydroxyurea withheld due to myelosuppression
(absolute neutrophil count <1000 x10^9/L) or platelet count (<80 x10^9/L) on two
consecutive evaluations. These data suggest that in low- and middle-income
settings, monthly or even quarterly routine CBC assessment for myelosuppression
associated with moderate fixed-dose hydroxyurea has limited clinical utility.

A total of 19 deaths occurred in the comparison group, with no death in the
treatment group. One death occurred in a child that was originally in the treatment
group, but the death occurred after the participant was withdrawn from the trial
because of progressive renal disease unrelated to study treatment. The death rate
in the comparison group was 2.0 per 100 person-years. There was no statistically
significant difference in the death rate between treatment and comparison groups ($p = 0.081$). The leading cause of death was suspected or confirmed malaria (defined as fever $\geq 37.5^\circ C$ in the presence of *Plasmodium falciparum* in peripheral blood smear or a positive rapid diagnostic antigen test) occurring in 79% of participants (15 of 19). As expected, we found a statistically significant lower incidence rate of uncomplicated, afebrile acute vaso-occlusive pain requiring hospitalization in the treatment group with hydroxyurea than in the comparison group, (5.3 per 100 person-years and 14.9 per 100 person-years, respectively, $p=0.002$). There was no difference in the incidence rates of febrile acute vaso-occlusive requiring hospitalizations. Incidence rates for other indications for hospitalization were described in Table 1. An early (3 months) and sustained (2 years) decrease in the initial abnormal TCD measurements was unexpected, but an important finding in our clinical trial, Figure 1. The results from this trial bolster pre-existing pooled data from 12 studies demonstrating that hydroxyurea therapy significantly lowers TCD.[6]

In Nigeria and other low- and middle-income settings, expenses for hydroxyurea therapy and laboratory monitoring are self-pay for the majority of families of children with SCA. To ensure the sustainability of stroke prevention efforts in low- and middle-income settings, minimizing costs and inconvenience of both treatment
and laboratory surveillance is critical. In our trial, hydroxyurea was produced locally, (Bond Chemical, Lagos Nigeria), and at a relatively inexpensive cost of approximately $5.00 United States dollars (USD) per month for the 20mg/kg/day dose per child. The cost of a CBC is $6.00 (USD), therefore minimizing CBC surveillance would potentially preserve family funds for hydroxyurea treatment. Our findings are similar to Baby HUG where moderate fixed-dose hydroxyurea therapy was not associated with absolute neutrophil count less than <500/mm³ or platelet count <80 ×10³/mm³.[7] Our study results did not reveal either laboratory nor clinical evidence of myelosuppression. Taken together, the results in this clinical trial and Baby HUG strongly suggest that monthly CBCs are not likely needed to identify myelosuppression at a moderate fixed-dose of hydroxyurea. Based on these data, the optimal CBC interval is undetermined.

In summary, the results of our NIH/NINDS-funded feasibility SPIN Trial provide additional evidence supporting the American Society of Hematology recommendation that for children with SCA and with abnormal TCD measurements living in a low- and middle-income settings, initial treatment with moderate fixed-dose hydroxyurea (~20 mg/kg/day) comparable to initial treatment with regular blood transfusion in STOP and superior to no treatment.[6] In addition, monthly
CBC assessments for myelosuppression associated with moderate fixed-dose hydroxyurea have limited clinical utility in low- and middle-income settings.

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**Conflict of Interest**

The authors declare that they have no conflicts of interest with the contents of this article.
References


Figure 1. Serial TCD measurements in children treated with hydroxyurea. Baseline, 3-month and 2-year TCD measurements in children receiving moderate fixed-dose hydroxyurea therapy (~20 mg/kg/day) for primary prevention of strokes. The highest time-averaged mean maximum velocity in the right and the left middle cerebral artery was obtained in 25 individuals assessed at baseline, 3 months, and 2 years after starting therapy, paired Wilcoxon signed rank test, baseline to 3 months (p<0.001); baseline to 2 years (p<0.001).
Table 1: Clinical and laboratory features of participants. Baseline characteristics and clinical outcomes in children with SCA and abnormal Transcranial Doppler (TCD) measurement (non-imaging greater than or equal to 200 cm/seconds) and comparison group (non-imaging < 200 cm/seconds) followed prospectively for 4.8 and 4.9 years.

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>All participants (n=235)</th>
<th>Comparison group (n=206)</th>
<th>Treatment group (n=29)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>8.1 (6.1 – 10.3)</td>
<td>8.2 (6.2-10.4)</td>
<td>7.0 (5.6-9.3)</td>
<td>0.067</td>
</tr>
<tr>
<td>Sex, male, percent (n)</td>
<td>46.4 (109)</td>
<td>46.1 (95)</td>
<td>48.3 (14)</td>
<td>0.827</td>
</tr>
<tr>
<td>Time followed, median (IQR) years</td>
<td>4.9 (4.6 – 5.2)</td>
<td>4.9 (4.6 – 5.2)</td>
<td>4.8 (3.7 – 5.6)</td>
<td>0.408</td>
</tr>
<tr>
<td>Ethnicity, Hausa-Fulani, percent (n)</td>
<td>89.8 (211)</td>
<td>91.7 (189)</td>
<td>75.9 (22)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Head of household university/professional education, percent (n), (n=230)</td>
<td>58.3 (134)</td>
<td>60.9 (123)</td>
<td>39.3 (11)</td>
<td>0.030</td>
</tr>
<tr>
<td>Height (cm), median (IQR)</td>
<td>124.0 (115.0 – 132.0)</td>
<td>126.0 (115.8-132.0)</td>
<td>120.0 (114.0-131.0)</td>
<td>0.227</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>20.0 (17.0 – 24.0)</td>
<td>20.0 (17.0-24.0)</td>
<td>20.0 (16.5-23.5)</td>
<td>0.576</td>
</tr>
<tr>
<td>BMI (kg/m2), mean (std. dev.)</td>
<td>13.4 (1.9)</td>
<td>13.4 (2.0)</td>
<td>13.7 (1.7)</td>
<td>0.534‡</td>
</tr>
<tr>
<td>TCD at baseline, (cm/sec), median (IQR)</td>
<td>140.0 (120.0 – 159.0)</td>
<td>134.0 (118.0-150.0)</td>
<td>208.0 (205.0-226.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>All hospitalizations per 100 person-years mean (std. dev.)</td>
<td>33.3 (40.7)</td>
<td>34.4 (41.4)</td>
<td>26.0 (36.6)</td>
<td>0.113†</td>
</tr>
<tr>
<td>Acute chest syndrome requiring hospitalization, per 100 person-years, mean (std. dev.)</td>
<td>1.42 (6.0)</td>
<td>1.53 (6.2)</td>
<td>0.76 (3.7)</td>
<td>0.566†</td>
</tr>
<tr>
<td>Acute vaso-occlusive pain requiring hospitalization, no associated fever, per 100 person-years, mean (std. dev.)</td>
<td>13.7 (24.2)</td>
<td>14.9 (24.9)</td>
<td>5.3 (17.2)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Acute vaso-occlusive pain requiring hospitalization with associated fever, per 100 patient/years, mean (std. dev.)</td>
<td>12.6 (19.8)</td>
<td>12.6 (20.0)</td>
<td>12.2 (18.4)</td>
<td>0.924†</td>
</tr>
<tr>
<td>Fever requiring hospitalization, no associated pain, per 100 patient/years, mean (std. dev.)</td>
<td>3.0 (8.5)</td>
<td>3.0 (7.4)</td>
<td>3.1 (13.9)</td>
<td>0.936†</td>
</tr>
<tr>
<td>Stroke, percent (n)</td>
<td>1.7 (4)</td>
<td>1.5 (3)</td>
<td>3.4 (1)</td>
<td>0.412*</td>
</tr>
<tr>
<td>Stroke, events per 100 patients/year, mean (std. dev.)</td>
<td>0.47 (2.8)</td>
<td>0.43 (3.0)</td>
<td>0.76 (3.9)</td>
<td>0.603†</td>
</tr>
<tr>
<td>Death, percent (n)</td>
<td>8.1 (19)</td>
<td>9.2 (19)</td>
<td>0.0 (0)</td>
<td>0.141*</td>
</tr>
<tr>
<td>Death, rate per 100 patients/year, mean (std. dev.)</td>
<td>1.8 (18.9)</td>
<td>2.0 (19.6)</td>
<td>0.0 (0.0)</td>
<td>0.081†</td>
</tr>
</tbody>
</table>

*Chi-square test for categorical variables or Mann-Whitney U test for continuous variables, unless otherwise noted.
# Fisher’s exact test
‡ T test
† Mid-p exact test

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