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Hydroxyurea Dose Escalation to Maximum Tolerated Dose in Pediatric Sickle Cell Disease: Hematologic and Clinical Outcomes in a Resource-Limited Setting in Cameroon. A Quasi-Experimental Study.

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ABSTRACT

Background:

Hydroxyurea (HU) dose escalation to maximum tolerated dose (MTD) has demonstrated superior fetal hemoglobin (HbF) induction in high-income settings, yet evidence from resource-limited sub-Saharan African contexts remains scarce. This study aimed to evaluate the hematologic, clinical safety, and feasibility of structured HU dose escalation to MTD in the paediatric SCD population in Cameroon.

Methods:

A quasi-experimental prospective single-arm study was conducted over 12 months (June 2024–June 2025) at Bonaberi Baptist Hospital Douala (BBHD), Cameroon. Thirty children aged 1–18 years with HbSS SCD receiving fixed-dose HU (15 mg/kg/day) were enrolled and escalated by 5 mg/kg/day every eight weeks toward MTD. Primary outcomes were %HbF and Hgb (g/dL). Secondary outcomes were frequencies of VOC, ACS, ED visits, and hospitalizations. Paired t-tests were used (significance: $p<0.05$).

Results:

Twenty-five of 30 participants (83.3%) completed the post-maximum tolerated dose phase (mean age: 9.4 ± 3.2 years; 60% female). Mean MTD achieved was 25.6 ± 3.4 mg/kg/day. HbF increased significantly from 20.3% ± 3.8 to 28.7% ± 4.1 ($p=0.03$), and Hgb improved from 9.6 ± 1.0
to 10.4 ± 0.8 g/dL ($p=0.04$). VOC frequency declined by 50% (1.2 ± 0.7 to 0.6 ± 0.4; $p=0.04$), ACS
by 66.7% (0.3 ± 0.2 to 0.1 ± 0.1; $p=0.05$), ED visits by 62.5% ($p=0.03$), and hospitalizations by 66.7% ($p=0.04$). No severe myelosuppression occurred.

Conclusions:

HU dose escalation to MTD is safe, feasible, and significantly improves hematologic and clinical outcomes in paediatric SCD in a resource-limited setting.

Recommendation:

Structured HU dose escalation to MTD under monthly CBC surveillance and clinician training on dose escalation protocol and safety should be incorporated into standard SCD care protocols at dedicated paediatric clinics in resource-limited African settings.

Keywords: *hydroxyurea; maximum tolerated dose; dose escalation; sickle cell disease; fetal hemoglobin; pediatric; resource-limited settings; Cameroon; Sub-Saharan Africa; vaso-occlusive crisis.*
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INTRODUCTION

Global Burden of Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy caused by a point mutation in the β-globin gene (Glu6Val), producing abnormal hemoglobin S (HbS) that polymerizes under deoxygenated conditions, leading to erythrocyte sickling, chronic hemolytic anemia, vaso-occlusion, and multi-organ damage (Kato et al., 2018). Globally, an estimated 300,000 infants are born with SCD annually, with approximately 75-90% in Sub-Saharan Africa (Piel et al., 2013). Nigeria alone accounts for roughly 100,000 new SCD births per year, and Cameroon has an HbS allele carrier frequency of 20-25% in the general population, with a disease prevalence of approximately 0.6% (Ngo et al., 2015). Despite representing the largest share of the global SCD burden, Africa has the fewest resources for disease management, and under-five mortality from SCD remains as high as 50-90% in poorly resourced settings (McGann, 2014).

Hydroxyurea: Mechanism and Evidence-Base

Hydroxyurea (HU), also known as hydroxycarbamide, is an oral ribonucleotide reductase inhibitor that elevates fetal hemoglobin (HbF) production through nitric oxide-mediated activation of soluble guanylyl cyclase and downstream γ-globin gene expression (Cokic et al., 2003). Elevated HbF inhibits HbS polymerization, reducing red cell sickling, hemolysis, and endothelial adhesion. The landmark Multicenter Study of Hydroxyurea (MSH) in adults (1995) and the BABY HUG trial in infants (2011) established HU's safety and efficacy, demonstrating significant reductions in painful crises, acute chest syndrome, and transfusion requirements (Charache et al., 1995; Wang et al., 2011). The REACH trial- a prospective study across four African countries subsequently confirmed HU's efficacy and safety in African children, reporting substantial reductions in VOC, ACS, malaria, and hospitalizations (Tshilolo et al., 2019). Despite this robust evidence base, HU remains underutilized across Africa, with prescription rates below 30% at most dedicated SCD clinics (Brandow & Panepinto, 2010).

Fixed-Dose versus Maximum Tolerated Dose Strategies

Two principal dosing strategies exist for HU therapy in SCD. The fixed-dose approach prescribes a standardized weight-based dose (typically 15-20 mg/kg/day) without subsequent titration, and is common in LMICs due to resource constraints and caution regarding toxicity (Yawn et al., 2014). The weighted-dose (MTD) or other dose escalation strategies like the more individualized approach via pharmacodynamically guided dosing introduce incremental increases, usually by 5 mg/kg/day every 8-12 weeks or through other pharmacodynamics measures to tailor the dose until mild hematologic suppression (neutrophil count approaching the lower safety limit) signals that maximal bone marrow engagement has been achieved (Ware et al., 2017). Multiple studies in high-income settings have demonstrated that MTD is associated with superior HbF induction, higher hemoglobin concentrations, and greater reductions in clinical events compared to fixed dosing (Ferster et al., 2001; Power-Hays et al., 2022). The NOHARM MTD trial confirmed that dose escalation to MTD significantly outperformed low-dose fixed therapy in HbF response in Ugandan children (John et al., 2020).

Evidence Gap and Study Rationale

Despite this evidence, structured MTD protocols have rarely been implemented in francophone West and Central Africa. Clinicians at facilities such as BBHD frequently prescribe fixed doses due to concerns about toxicity monitoring capacity, drug costs, and institutional infrastructure (Okocha et al., 2022; Segbefia et al., 2021). The absence of a locally validated evidence base for MTD titration in Cameroon represents a significant implementation gap, as national SCD guidelines in Cameroon and many neighboring countries do not currently recommend individualized dose escalation. This study directly addresses this gap by evaluating the hematologic and clinical outcomes of HU dose escalation to MTD in a resource-limited Cameroonian pediatric SCD clinic, with the primary aim of generating evidence to inform contextually appropriate clinical protocols.

METHODS

Study Design and Setting

A prospective, single-arm quasi-experimental study was conducted from June 2024 to June 2025 (12 months) at the Sickle Cell Disease Clinic of the Bonaberi Baptist Hospital Douala (BBHD), Cameroon. BBHD is a mission hospital serving a predominantly low-income peri-urban population in the Bonaberi district of Douala IV. The SCD clinic operates monthly and manages over 200 HU-treated pediatric patients. The study conformed to the Declaration of Helsinki (World Medical Association, 2013). Due to the single-arm open-label nature of the study, blinding was not applicable.

Sample Size and Randomization

Sample size was calculated using the paired t-test formula for a single-arm pre-post comparison.

$n = [(z_{(\alpha/2)} + z_{\beta})^2 \times \sigma^2] \div \delta^2$

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Where:
δ: Represents the expected mean within-patient change in %HbF (8.0%),
σ: Is the anticipated standard deviation of that change (10.0%) derived from prior African pediatric SCD literature (REACH trial (SD range: 8.2–11.4%) and by John et al. (2020) in the NOHARM dose escalation study in Uganda (SD = 9.8%)
$z_{(\alpha/2)} = 1.96$ (two-tailed $\alpha = 0.05$) $z_{\beta} = 0.842$ (power = 80%).
Substituting values;
$n = [(1.96 + 0.842)^2 \times (10.0)^2] \div (8.0)^2 (1.96 + 0.842)^2 = (2.802)^2 = 7.851$
$785.1 \div 64 = 12.27$ n = ~13.0
Adjust for expected attrition: n_adjusted = n_raw ÷ (1 − attrition rate)
n_adjusted = 13 ÷ (1 − 0.15)
= 13 ÷ 0.85
n_adjusted = 15.29 = ~16
Apply the practical safety margin.
The study doubled the minimum to maximize representativeness and robustness. Therefore, 2 × 16 = 32 (rounded down to the nearest 5-unit boundary). Practical n = 30
Verification of power retained at n=30
Achieved power = $\Phi[(\delta\sqrt{n} / \sigma) - z_{(\alpha/2)}]$
$= \Phi[(8.0 \times \sqrt{30} / 10.0) - 1.96]$
$= \Phi[(8.0 \times 5.477 / 10.0) - 1.96]$
$= \Phi[4.382 - 1.96]$
$= \Phi[2.422]$
$= 0.9923 \rightarrow$ 99.2% power

Participants

Eligibility criteria

- Confirmed HbSS SCD by hemoglobin electrophoresis
- Age 1-18 years
- Minimum six months on a fixed HU dose of 15 mg/kg/day with documented clinic attendance
- No blood transfusion within the preceding three months
- Baseline hematologic stability (ANC >2,000/μL; platelets >80,000/μL; reticulocytes >80,000/μL where Hgb <9 g/dL)
- Parent/guardian provision of written informed consent. Children with documented renal or hepatic impairment, severe comorbidities, HU toxicity history, or concurrent enrollment in other trials were excluded.

Dose Escalation Protocol

After confirming baseline eligibility, HU was escalated from 15 mg/kg/day by increments of 5 mg/kg/day every eight weeks until MTD was reached (Ware et al., 2017). Doses were rounded to the nearest 50 mg or 100 mg based on available tablet strengths and pediatric pharmacist review. The MTD was defined as the highest dose tolerated without development of severe cytopenia: ANC >2,000/μL, platelets >80,000/μL, and reticulocytes >80,000/μL when Hgb <9 g/dL (Yawn et al., 2014). Where MTD criteria were met, escalation was discontinued and the dose maintained. Dose reduction (by 2.5-5 mg/kg/day) was implemented if any safety threshold was approached. The theoretical maximum dose cap was 35 mg/kg/day as per Medscape pediatric SCD protocol.

Outcome Measures

The primary outcomes were: (1) percentage fetal hemoglobin (%HbF), quantified by high-performance liquid chromatography (HPLC); and (2) total hemoglobin concentration (Hgb, g/dL), measured by automated Mindray BC-5150 29-parameter hematology analyzer. Secondary outcomes were cumulative twelve-month frequencies of: VOC episodes (defined as acute pain episodes requiring medical evaluation or analgesic administration); ACS events (new pulmonary infiltrate on chest radiograph with fever and/or respiratory symptoms); ED visits; and hospitalizations. All outcomes were compared between the fixed-dose baseline and the 12-month post-MTD phase.

Statistical Analysis

Data were entered and managed in Microsoft Excel (v.19) and analyzed in IBM SPSS Statistics version 25. Continuous variables were summarized as means ± standard deviations (SD). Within-group pre–post comparisons used paired sample t-tests, with statistical significance defined at $p<0.05$ (two-tailed). Effect sizes were estimated using Cohen's d. All participants who completed post-MTD assessments were included in the primary analysis.

Ethics and Patient Consent

Ethical clearance was obtained from the University of Port Harcourt Research Ethics Committee (Ref: UPH/CEREMAD/REC/MM102/021; approval date: 24 September 2024) and the Cameroon Baptist Convention (CBC) Health Board Institutional Review Board (Ref: IRB2023-62; approval date: 31 May 2024). Written informed consent was obtained from parents/legal guardians of all participants before enrolment; assent was sought from children aged ≥7 years. Data were de-identified and stored on password-protected devices accessible only to named investigators.

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RESULTS

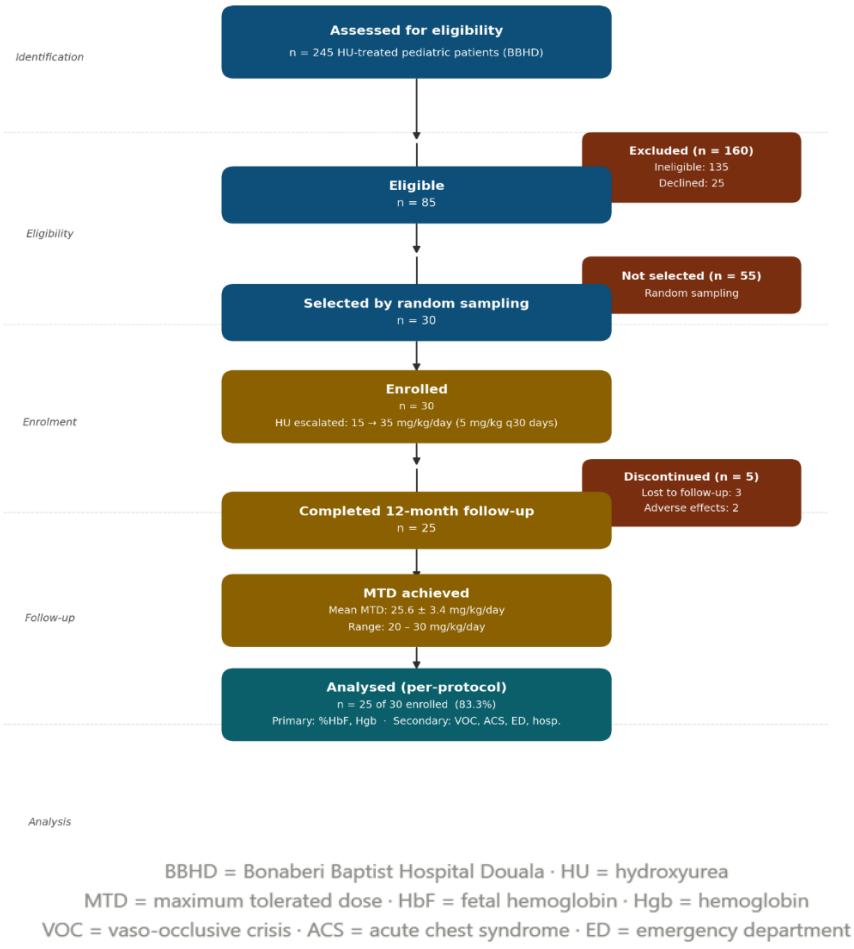

Figure 1. CONSORT participant flow diagram

Participant Flow and Characteristics

Of 30 enrolled participants, 25 (83.3%) completed the twelve-month post-MTD assessment phase. Five participants were excluded from the final analysis: three due to loss to follow-up and two due to severe adverse (nausea/vomiting) effect to HU. Baseline characteristics of completers are presented in Table 1. The mean age was 9.4 ± 3.2 years (range: 3–17 years). The sex distribution was 60% female and 40% male. All participants had confirmed HbSS genotype. The mean MTD achieved was 25.6 ± 3.4 mg/kg/day (range: 20–30 mg/kg/day), representing a mean dose increase of 10.6 mg/kg/day above the 15 mg/kg/day fixed baseline.

Table 1. Participant characteristics and baseline features (n=25)

Characteristic	n / Value	Percentage (%)	Notes
Age (years), mean ± SD	9.4 ± 3.2	—	*Range: 1–18 yrs*
Male	10	40.0	
Sex			—
Female	15	60.0	

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SCD genotype (HbSS)	25	100.0	*All homozygous*
Baseline HU dose (mg/kg/day)	15.0 (fixed)	—	*Pre-escalation*
Mean MTD achieved (mg/kg/day)	25.6 ± 3.4	—	*Range: 20–30*
Completers (of 30 enrolled)	25	83.3	*3 lost to F/U* *2 adverse effects*

SD = standard deviation; HU = hydroxyurea; MTD = maximum tolerated dose; F/U = follow-up; HbSS = homozygous sickle cell disease.

Hematologic Outcomes

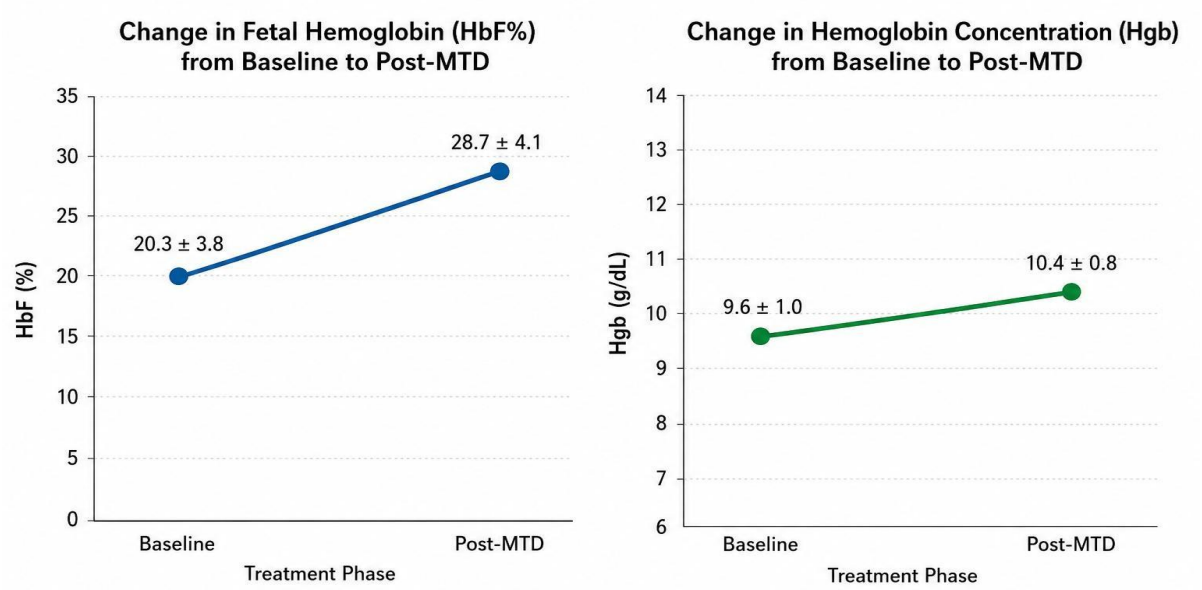
Mean HbF increased significantly from 20.3% ± 3.8 at baseline to 28.7% ± 4.1 post-MTD (Δ = +8.4%; p=0.03), representing a 41.4% relative increase. Mean Hgb improved from 9.6 ± 1.0 g/dL to 10.4 ± 0.8 g/dL (Δ = +0.8 g/dL; p=0.04), consistent with improved erythropoietic activity and attenuated hemolysis. These improvements were observed across all age groups and both sexes, with no significant effect modification by sex. Full hematologic data and graphical representation of the change in baseline HbF (%) and Hgb (g/dL) are presented in Table 2 and Figures 2 and 3 below.

Table 2. Hematologic outcomes before and after HU dose escalation to MTD (n=25)

Parameter	(Mean ± SD)	D (Mean ± SD)	Δ Change	p-value
Fetal hemoglobin, HbF (%)	20.3 ± 3.8	28.7 ± 4.1	**+8.4%**	**0.03**
Hemoglobin conc., Hgb (g/dL)	9.6 ± 1.0	10.4 ± 0.8	**+0.8**	**0.04**
Mean HU dose (mg/kg/day)	15.0 (fixed)	25.6 ± 3.4	**+10.6**	—

HbF = fetal hemoglobin; Hgb = hemoglobin concentration; MTD = maximum tolerated dose; p<0.05 (paired t-test); Δ Change = post-MTD value minus baseline value.

Figure 2: Change in fetal hemoglobin (%HbF) and hemoglobin concentration (Hgb, g/dL) from baseline to post-MTD (12 months).



Values are mean ± standard deviation (SD). MTD = maximum tolerated dose. HU = hydroxyurea. Δ Change = post-MTD value minus baseline value. Asterisk () denotes statistical significance at p < 0.05.

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Clinical Outcomes

All four clinical event frequencies declined following MTD escalation (Table 3). VOC episodes fell by 50% per participant (1.2 ± 0.7 to 0.6 ± 0.4; p=0.04). ACS episodes declined by 66.7% (0.3 ± 0.2 to 0.1 ± 0.1; p=0.05). ED visits decreased by 62.5% (0.8 ± 0.4 to 0.3 ± 0.2; p=0.03) and hospitalizations by 66.7% (0.6 ± 0.3 to 0.2 ± 0.1; p=0.04). The concurrent reduction across all four clinical endpoints suggests a systemic benefit attributable to improved HbF-mediated inhibition of HbS polymerization.

Table 3. Clinical outcomes before and after HU dose escalation to MTD (n=25)

Clinical Outcome	(Mean ± SD)	D (Mean ± SD)	% Reduction	p-value
Vaso-occlusive crises (VOC)	1.2 ± 0.7	0.6 ± 0.4	**50.0%**	**0.04**
Acute chest syndrome (ACS)	0.3 ± 0.2	0.1 ± 0.1	**66.7%**	0.05
Emergency department visits	0.8 ± 0.4	0.3 ± 0.2	**62.5%**	**0.03**
Hospitalizations	0.6 ± 0.3	0.2 ± 0.1	**66.7%**	**0.04**

VOC = vaso-occlusive crisis; ACS = acute chest syndrome; ED = emergency department; p<0.05 (paired t-test); % Reduction = ([Baseline − Post-MTD] / Baseline) × 100.

Safety Monitoring

Safety parameter monitoring was conducted monthly throughout the escalation phase. Two participants were discontinued from the study following development of severe nausea after successive dose escalation steps and were excluded from the per-protocol analysis. This gastrointestinal intolerance did not involve any breach of hematologic safety thresholds and is therefore captured in the CONSORT participant flow diagram rather than in Table 4, which reports hematologic safety parameters exclusively. Among the 25 participants who completed the study, no hematologic safety threshold breach was recorded across any monitored parameter throughout the escalation phase, as detailed in Table 4. No severe myelosuppression occurred, and no dose holds or down-titrations were required. These findings confirm the safety profile of structured MTD escalation under monthly CBC surveillance in this population.

Table 4. Hematologic safety monitoring summary during dose escalation (n=25)

Safety Parameter	Safety Threshold	Breaches Recorded	Action Taken
Absolute neutrophil count (ANC)	>2,000/µL	**0**	No dose holds required.
Platelet count	>80,000/µL	**0**	No dose holds required
Reticulocyte count	>80,000/µL	**0**	No dose holds required
Severe myelosuppression	N/A	**0**	No events recorded

ANC = absolute neutrophil count; All parameters assessed monthly throughout the twelve-month escalation phase.

DISCUSSION

Principal Findings in Context

This study provides prospective evidence that HU dose escalation to MTD is both safe and clinically effective in children with SCD attending a resource-limited clinic in Cameroon. The 8.4% absolute increase in HbF (from 20.3% to 28.7%) and the 0.8 g/dL Hgb improvement observed following MTD escalation align closely with findings from the NOHARM MTD trial, which reported mean HbF of 29% at MTD (mean 28.3 mg/kg/day) in Ugandan children (John et al., 2020), and with the REACH trial, which demonstrated sustained HbF elevation of >20% across four African nations following HU initiation at standard doses (Tshilolo et al., 2019). The present study extends these findings to a francophone Central African context not previously represented in the MTD literature.

Dose-Response and HbF Threshold

The mean MTD of 25.6 mg/kg/day achieved in this study falls within the 25–30 mg/kg/day range identified by Ware et al. (2017) as effective and well-tolerated in pediatric SCD. The observed HbF levels (28.7% post-MTD) approach the ≥30% HbF threshold identified by Quinn and others as the minimum for clinically meaningful HbS polymer dissolution (Quinn et al., 2021). This suggests that further dose optimization beyond 25.6 mg/kg/day, if tolerated and

supported by adequate monitoring, may produce additional HbF gains and further reduce clinical event rates. Ferster et al. (2001) similarly reported HbF levels exceeding 25% in children maintained on HU for five or more years at doses approaching MTD, emphasizing that duration of therapy compounds dose-related benefits over time.

Clinical Benefits: VOC, ACS, and Healthcare Utilization

The 50% reduction in VOC and 66.7% reductions in ACS and hospitalizations observed here are consistent with the mechanistic understanding that HbF elevation directly attenuates HbS polymerization, erythrocyte rigidity, and endothelial adhesion, which are all the primary pathophysiologic drivers of vaso-occlusive events (Steinberg et al., 2003). Wang et al. (2011) reported similar reductions in VOC and hospitalizations in the BABY HUG cohort, and Charache et al. (1995) demonstrated a 44% reduction in painful crises among adult MSH trial participants. The healthcare utilization benefits observed in this study — particularly the 62.5% reduction in ED visits carry significant cost implications in a low-income setting where each emergency visit represents a substantial household economic burden. These findings support arguments made by McGann (2014) and Brandow & Panepinto (2010) that HU underutilization in Africa constitutes a healthcare equity failure with preventable human and economic costs.

Safety and Feasibility in Resource-Limited Settings

A central concern inhibiting MTD adoption in LMICs is the perceived risk of hematologic toxicity under conditions of limited monitoring infrastructure (Okocha et al., 2022). The complete absence of safety threshold breaches across 25 participants and twelve months of dose escalation in this study despite the modest laboratory environment at BBHD provides meaningful evidence that structured gradual escalation with monthly CBC monitoring is safe in this context. This finding is consistent with Agumadu et al. (2020), who demonstrated HU safety across Nigerian pediatric SCD cohorts receiving doses up to 18.5 mg/kg/day, and with the REACH trial safety data (Tshilolo et al., 2019). Monthly monitoring of ANC, platelet count, and reticulocyte count, all achievable with an automated hematology analyzer, appears sufficient to safely support MTD titration. Two participants (6.7%) discontinued due to severe nausea following successive dose escalation steps, consistent with the known gastrointestinal side effect profile of hydroxyurea at higher doses reported by Ware et al. (2017) and Yawn et al. (2014). This underscores the importance of patient counselling and gradual dose titration in MTD escalation protocols, particularly in pediatric populations where treatment tolerability directly affects adherence and retention.

Barriers to MTD Implementation in Africa and Implications

Despite the evidence presented here, structural barriers to MTD implementation in African SCD programs remain significant. These include drug affordability, incomplete supply chains, inadequate clinician training on dose titration protocols, and persistent myths about HU carcinogenicity that deter both prescribers and families from pursuing higher doses (Segbefia et al., 2021; Okocha et al., 2022). The WHO Model List of Essential Medicines' inclusion of HU since 2017 provides a policy framework within which LMIC-based evidence, such as that generated by this study, can inform national SCD guideline revision. However, translating this evidence into practice across Cameroon, Nigeria, and the broader ECOWAS/CEMAC region will require health system attention to clinician training, laboratory capacity, and drug subsidy mechanisms; all areas that future implementation research should directly address.

Generalizability (External Validity)

The generalizability of this study's findings warrants careful consideration. The study was conducted at a single dedicated SCD clinic in Douala, Cameroon, which is a peri-urban mission hospital serving a predominantly low-income population in francophone Central Africa. The demographic, clinical, and infrastructural characteristics of BBHD are broadly representative of mission and district hospital-level SCD care across urban and peri-urban sub-Saharan Africa, where most paediatric SCD patients in the region receive care. The mean patient age (9.4 ± 3.2 years), HbSS genotype prevalence, baseline HU dose (15 mg/kg/day), and access to automated haematology analysis are consistent with conditions at comparable facilities in Nigeria, Uganda, and the Democratic Republic of Congo, as reported by the REACH trial (Tshilolo et al., 2019). The findings are therefore likely applicable to similar resource-limited paediatric SCD programmes across Cameroon and the broader ECOWAS/CEMAC region. Caution is warranted in generalising to high-income settings with different infrastructure, pharmacogenomic profiles, or baseline HU exposure levels, and to rural African settings with more limited laboratory capacity than BBHD. Multicentre replication across diverse LMIC contexts will be essential to fully characterise the external validity of these findings.

Conclusions

HU dose escalation to MTD significantly improved hematologic indices and reduced clinical complications in

children with SCD in a resource-limited Cameroonian hospital setting. The 41% relative increase in HbF, concomitant hemoglobin improvement, and reductions of 50–67% across all clinical event categories, achieved without any hematologic safety breaches, constitute compelling evidence for the safety and efficacy of structured MTD titration in this population. These findings should inform the revision of SCD clinical management protocols in BBHD, CBCHS, Cameroon, and across Sub-Saharan Africa, with particular emphasis on the integration of individualized, MTD-based HU dosing supported by standardized monthly CBC monitoring. Wider implementation of this approach has the potential to substantially reduce SCD morbidity, healthcare utilization, and preventable mortality across the region.

Limitations

This study has several limitations that should be acknowledged. First, the sample size of 25 for analysis, while statistically adequate for the primary outcome as demonstrated by the achieved power of 99.2%, restricts the precision of secondary outcome estimates and may not fully capture the clinical and biological variability present across the broader Cameroonian pediatric SCD population. Second, the twelve-month post-MTD observation window may be insufficient to characterize long-term HbF stability, late hematologic toxicity, or the durability of clinical event reductions. Third, the single-centre design limits generalizability to other LMIC contexts with different laboratory and clinical infrastructure. Fourth, the absence of a concurrent control group limits causal inference; the prospective within-patient pre-post comparison design is a pragmatic and ethically appropriate alternative that minimises selection bias while acknowledging this constraint. Future multicentre randomised controlled trials with longer follow-up durations are needed to confirm and extend these findings.

Recommendations

Based on the findings, the study recommends that structured HU dose escalation to MTD under monthly CBC surveillance should be incorporated into standard SCD care protocols at dedicated paediatric clinics in resource-limited African settings. National SCD care guidelines across Cameroon, Nigeria, and the ECOWAS/CEMAC region should be revised to include individualised weight-based MTD dosing protocols, supported by investment in laboratory infrastructure, HU cost subsidisation, and structured clinician training programmes addressing persistent barriers to MTD implementation. Multicentre randomised controlled trials with a minimum 24-month follow-up are needed to confirm the long-term durability of HbF gains, define optimal MTD targets across age groups, and establish the cost-effectiveness of MTD escalation relative to adherence-based fixed-dose strategies in diverse LMIC settings.

List of abbreviations

%HbF — Percentage fetal hemoglobin
ACS — Acute chest syndrome
ANC — Absolute neutrophil count
BBHD — Bonaberi Baptist Hospital Douala
CBC — Complete blood count
CEMAC — Economic Community of Central African States
ECOWAS — Economic Community of West African States
ED — Emergency department
HbS — Hemoglobin S (sickle hemoglobin)
HbSS — Homozygous sickle cell genotype
Hgb — Hemoglobin concentration
HU — Hydroxyurea (hydroxycarbamide)
HUEG — Hydroxyurea Escalation Group
IRB — Institutional Review Board
LMIC — Low- and middle-income country
MTD — Maximum tolerated dose
SCD — Sickle cell disease
SD — Standard deviation
SPSS — Statistical Package for the Social Sciences
VOC — Vaso-occlusive crisis

Ethics Approval and Consent

Ethical clearance was obtained from the Cameroon Baptist Convention Health Board Institutional Review Board and the University of Port Harcourt Research Ethics Committee. Written informed consent was obtained from parents or legal guardians of all participants before enrolment, in accordance with the Declaration of Helsinki.

Availability of Data

De-identified study data are available from the corresponding author on reasonable request.

Authors' Contributions

CP: study conception, design, data collection, analysis, and manuscript writing. EPO, BAA: supervisory oversight, critical manuscript revision. All authors approved the final version.

Conflict of Interest

The authors declare no conflict of interest related to this research.

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AI Assistance Disclosure

Artificial intelligence tools, specifically Claude (Anthropic, claude.ai), were used during the preparation of this manuscript to assist with proofreading, grammar and consistency checking, academic language editing, and structural formatting. All scientific content, data, analyses, interpretations, and conclusions are the sole responsibility of the authors. The AI did not contribute to study design, data collection, statistical analysis, or intellectual conceptualization of the research. The authors reviewed and approved all AI-assisted edits and take full responsibility for the integrity and accuracy of the final manuscript.

Trial Registration

This trial was not registered in a formal clinical trial registry at the time of commencement. The study protocol is available from the corresponding author on request.

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