

Original Article

Hydroxyurea therapy for children with sickle cell anemia: A systematic review and meta-analysis

Firyal Khansa^{1*}, Muhammad H. Ghifari¹, Muhammad B. Daffa¹, Fiola Nasywa¹, Seyi S. Enitan², Itodo G. Elejo³ and Mazen EI. Ali⁴

¹Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; ²Department of Medical Laboratory Science, Babcock University, Ilishan-Remo, Nigeria; ³Department of Microbiology, Federal Teaching Hospital, Lokoja, Nigeria; ⁴Faculty of Medicine, Minia University, Minia, Egypt

*Corresponding author: firyaalkhansaa@gmail.com

Abstract

Sickle cell anemia (SCA) is a major global health issue, particularly among pediatric population, influenced by factors such as malaria susceptibility and genetic distribution. On the other hand, hydroxyurea therapy has been a well-established and accepted treatment for SCA, with over 25 years of clinical experience. It has been proven to be safe and effective in preventing vaso-occlusive events and chronic organ damage. The aim of this study was to assess the efficacy of hydroxyurea in alleviating pediatric SCA. This study was comprised of a systematic literature search and meta-analysis in accordance with the PRISMA and the Cochrane Handbook guidelines. A systematic search was performed on PubMed, Cochrane, and ScienceDirect databases for relevant literature published as of January 2024. Placebo-controlled clinical trials reporting the efficacy of hydroxyurea in managing SCA among pediatric patients were included in the systematic review. The eligible studies were further assessed for its reporting quality using Risk of Bias 2.0. Pooled analysis was carried out using a random effect model, where the effect size was calculated based on the mean difference (MD) and 95% confidence interval (95%CI). Three randomized clinical trials comprised of 423 participants were included in the studies. Among patients receiving hydroxyurea, significant improvement was observed in fetal hemoglobin (HbF) with MD of 9.45% (95%CI: 2.15–16.75), but not in mean corpuscular volume (MCV) (MD=8.77 fL (95%CI: -28.85–46.39)). Hydroxyurea also significantly reduced white blood cell (WBC) (MD=-4.21 cells/mm³; 95%CI: -5.68--2.93), absolute neutrophil count (ANC) (MD=-1.43 cells/mm³; 95%CI: -2.11--0.74), absolute reticulocyte count (ARC) (MD=-141.85 cells/mm³; 95%CI: -172.77--110.94), and platelet count (MD=-74.92 cells/mm³; 95%CI: -117.05--32.78). In conclusion, hydroxyurea is efficacious in treating pediatric SCA, as observed in the HbF, WBC, ANC, ARC, and platelet count.

Keywords: Anemia, hydroxyurea, meta-analysis, pediatric, sickle cell

Introduction

Sickle cell disease (SCD) is a serious, inherited blood disorder that significantly impacts global health, with an estimated 100,000 individuals affected in the United States and millions worldwide [1]. This condition includes a range of congenital hemolytic anemias characterized by the predominance of sickle hemoglobin (HbS). The disease arises from a single mutation in the beta-globin gene, which results in the substitution of glutamic acid with valine at position six of



the beta-globin chain. This genetic alteration leads to the formation of abnormal HbS tetramers, which, under deoxygenated conditions, undergo rapid polymerization, damaging erythrocyte membranes and causing them to assume a rigid, sickle shape [2,3]. These sickled cells have a markedly reduced lifespan and lead to both acute and chronic hemolysis, as well as vaso-occlusive events that obstruct blood flow, cause tissue hypoxia, and contribute to significant morbidity and early mortality [4,5]. A systematic review suggested that among patients with sickle cell disease (SCD), severe malocclusion requiring orthodontic intervention is often observed [6]. Dysregulation of cholesterol among patients with SCA was found to be correlated with vaso-occlusive seizures and acute thoracic syndrome [7]. The prevalence is found to be higher among people of color, as compared to Caucasians [8]. The clinical manifestations of this disease were found to be different among races and ethnicities [8].

Sickle cell anemia (SCA), the most severe form of SCD, is characterized by homozygosity for the HbS mutation, while other forms include HbSC and HbS β^0 thalassemia [9,10]. In resource-rich settings such as the United States and Europe, newborn screening and preventive treatments, including penicillin prophylaxis and vaccinations, have significantly reduced early mortality [2,11]. However, in resource-limited areas, the burden of SCD remains high due to inadequate diagnostic and preventive measures, leading to elevated childhood mortality rates [12]. Most of the achievement in reducing the burden of SCA is due to the introduction of hydroxyurea [13]. In a cost-effectiveness evaluation based on the conditions in African countries, the addition of hydroxyurea to the standard care of SCA could reduce disability-adjusted life years by 1.37 and save USD 191 per individual [14]. In a systematic review, the use of hydroxyurea in SCA management could alleviate the economic burdens on patients and healthcare systems [15]. Studies have suggested that the early introduction of hydroxyurea to SCA management in pediatric patients can potentially result in better outcomes [16,17].

The efficacy of hydroxyurea is due to its ability to induce fetal hemoglobin (HbF), which inhibits the polymerization of HbS and mitigates sickling [18]. A systematic review comprised of 9 randomized controlled trials (RCTs) participated by 1,104 patients revealed that hydroxyurea is effective in improving pain management, reducing neutrophil counts, and increasing HbF levels among general SCA patients [19]. Since its introduction in the 1990s, hydroxyurea has been associated with improvements in laboratory parameters, reduction in acute complications like vaso-occlusive events and acute chest syndrome, and decreased need for blood transfusions and hospitalizations [20]. Recent guidelines advocate for its broader use, including in infants as young as nine months [21]. Despite its proven efficacy and an acceptable safety profile, concerns persist regarding its long-term effects and optimal application, particularly in diverse patient populations and across varying disease severities. The aim of this study was to comprehensively evaluate the efficacy of hydroxyurea in managing SCA among pediatric patients.

Methods

Study design and search strategy

This meta-analysis and systematic review were carried out in accordance with the PRISMA statement and the Cochrane Handbook for Systematic Reviews of Interventions, version 6.3, 2022 [22,23]. The aim of this review was to evaluate the efficacy of hydroxyurea in managing SCA among pediatric patients based on HbF, mean corpuscular volume (MCV), and other outcomes such as absolute neutrophil count (ANC), absolute reticulocyte count (ARC), white blood cell count (WBC), and platelet count.

This systematic review used the search engine from PubMed, ScienceDirect, and Cochrane to identify RCTs investigating the efficacy of hydroxyurea for sickle cell anemia in children among pediatric patients as of January 2024. The keywords combination was arranged using Boolean operators “AND” and “OR”, along with the terms from medical subject headings (MeSH). The keywords combination was as follows: (Hydroxyurea) AND (“Sickle Cell” OR “Sickle Cell Anemia”) AND (Child OR Pediatric OR children OR “young children”). No restriction on the publication date.

Study eligibility criteria

The inclusion and exclusion criteria were established based on the PICOS (population, intervention, control, outcome, and study design). The population was pediatric patients aged under 13 years who received a clinical diagnosis of SCA confirmed by hemoglobin electrophoresis. The intervention was hydroxyurea in addition to the standard of care, while a placebo was used as the control. Studies should measure HbF and MCV as the primary outcomes, while ANC, ARC, WBC, and platelet count were considered as the secondary outcomes. We only include studies adopting RCTs design. Reviews, case reports, conference abstracts, animal trials, and non-English papers were excluded.

Screening and selection

Duplicate removal was performed automatically on Zotero 6.0.30 after importing all searched records into the software. Thereafter, the screening was carried out based on the title and abstract, followed by the full content screening based on the eligibility criteria stated previously. The whole screening and selection process was performed independently by two reviewers (M.B.D. and M.H.G.). The included studies in the final stage should be approved by the consensus agreement from the two reviewers. Any discrepancies that emerged were resolved by re-checking the articles, discussion, and consultation with the third reviewer (F.K.).

Data extraction and quality appraisal

The study used a predetermined outcome sheet in tabular form to extract data from the included studies. The table contained the following column headings: (1) author and year of publication; (2) study location, center, and duration; (3) study population including sample size and type of subjects; (4) intervention and control including the uptake dosage and frequency; (5) study outcome. Two reviewers (M.B.D. and M.H.G.) quantitatively evaluated the studies, while another author (F.K. and F.N.) double-checked the retrieved data. The risk of bias was evaluated using the Cochrane 5.2.0 Risk of Bias Tools, which consists of five domains for studies [24]. Four reviewers separately assessed the quality and any disagreements were settled by consensus between the reviewers.

Quantitative data analysis

Statistical analysis was carried out utilizing Cochrane Collaboration - Review Manager 5.4.1. The mean difference (MD), 95% confidence interval (95%CI), and *p*-value were calculated for data generated from Hb, HbF, ARC, ANC, MCV, WBC, and platelet counts. The pooled estimates were performed under the DerSimonian-Laird random-effects model. The I^2 index was used as a measure in determining the level of heterogeneity in meta-analysis [25]. We followed the recommendation by Higgins and colleagues suggesting that low, moderate, and high heterogeneities were indicated by I^2 values of 25%, 50%, and 75%, respectively [26].

Results

Search results and characteristics of the included studies

The PRISMA flow diagram for the included studies based on the eligibility criteria in this review is presented in **Figure 1**. The initial identification yielded 1867 records, of which 787 were identified as duplicates and removed. The title and abstract screenings were performed on 1080 records, where 957 were removed due to irrelevance. Among 54 retrievable full-text articles, 5 did not recruit control group, 38 were review articles, 1 was not relevant due to the patient's age, 6 did not report the outcomes of interest, and 1 was an animal study. Three RCTs involving 423 pediatric patients in the intervention group and control group were finally included in the systematic review and meta-analysis [27-29]. Among these studies, the average age of participants ranged from 9 months to 11 years old. The research was conducted in Uganda (n=1) and the United States (n=2) and published between 2011 and 2017. A summary of the characteristics of the included studies, along with their outcomes, is presented in **Table 1**.

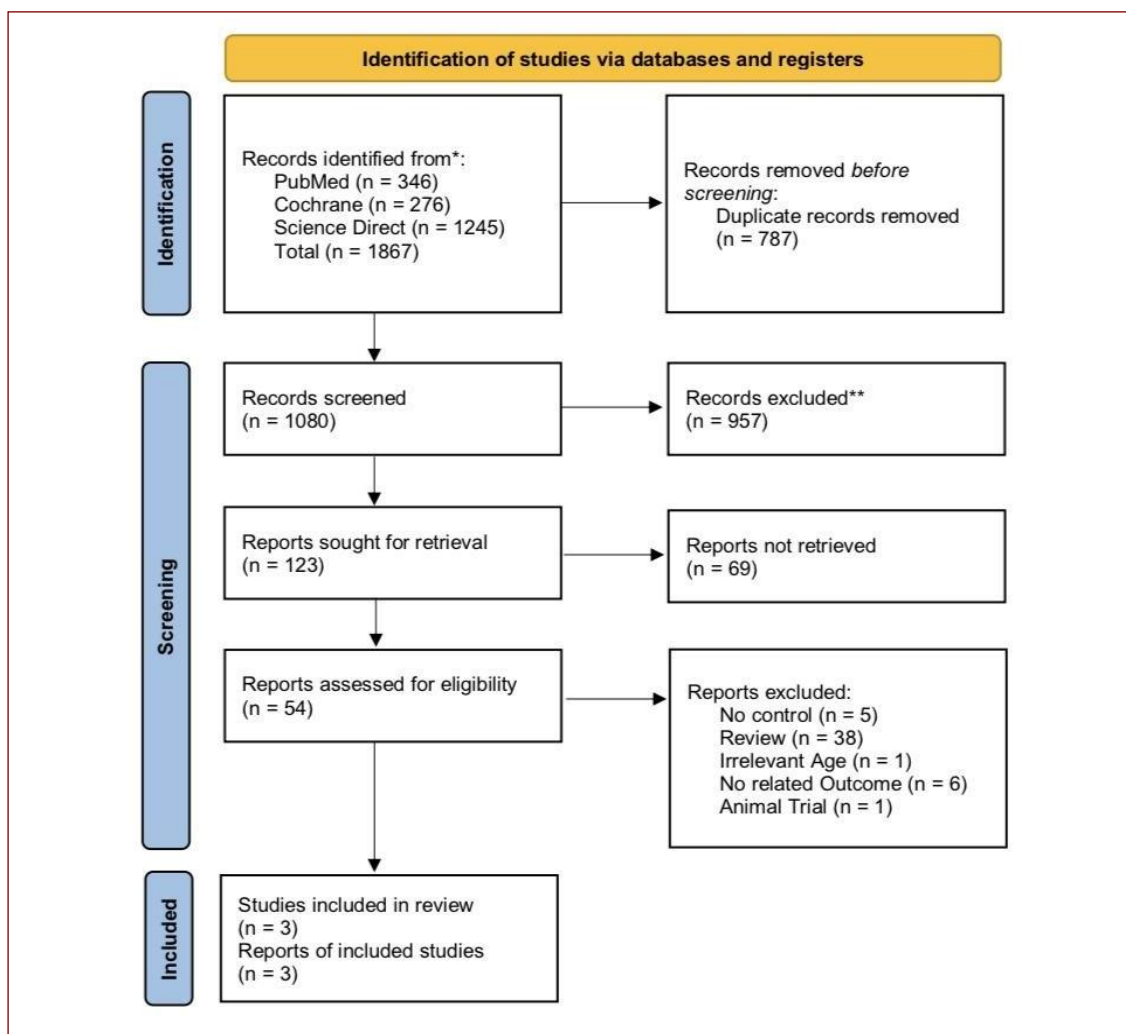


Figure 1. PRISMA diagram for the screening and selection process of the published studies.

Table 1. Characteristics and outcomes of the included randomized clinical trials

Author, year	Characteristics	Intervention (HU vs placebo)	Outcomes
Wang <i>et al.</i> , 2011 [27]	n=97 versus 96 Age: 9–18 months	20 mg/kg/day for 2 years	HbF, MCV, WBC, ANC, ARC, platelet count
Opoka <i>et al.</i> , 2017 [29]	n=104 versus 104 Age: 1–4 years	20±2.5 mg/kg/day for 12 months	HbF, MCV, WBC, ANC, ARC platelet count
Hankins <i>et al.</i> , 2015 [28]	n=11 versus 11 Age: 2–11 years	20–35 mg/kg/day for 30 months	HbF, MCV, WBC, ANC, ARC, platelet count

ANC: absolute neutrophil count; ARC: absolute reticulocyte count; HbF: fetal hemoglobin; HU, hydroxyurea; MCV: mean corpuscular volume; WBC: white blood cell count

Risk of bias of the included studies

The results of the risk of bias analysis for each included study are presented in **Figure 2**. All three studies performed randomized sequence generation and concealed the allocation process [27–29]. Two studies blinded the participants [27,29], and only one study had an unclear blinding mechanism [28]. Furthermore, there were two studies blinding the assessor when measuring the outcome [27,29], while only one study was unclear [28]. Two studies reported the complete outcome [27,29], except for one study having incomplete outcome data [28]. Overall, two studies reported the data selectively [27,29], while only one study was unclear [28].

Effects on HbF and MCV

Three studies that are reporting HbF and MCV [27–29]. The results of the random-effect pooled estimates on the two outcomes comparing the hydroxyurea and placebo are presented in **Figure 3A** and **3B**. For the HbF, the pooled effect was significant with an MD of 9.45% (95%CI: 2.15–16.75) and $p=0.01$. Meanwhile, hydroxyurea was found to have no significant effect on MCV

($p=0.65$), where the MD was 8.77 fL (95%CI: -28.85–46.39). The heterogeneity for both outcomes was negligible, as indicated by $I^2=0\%$.

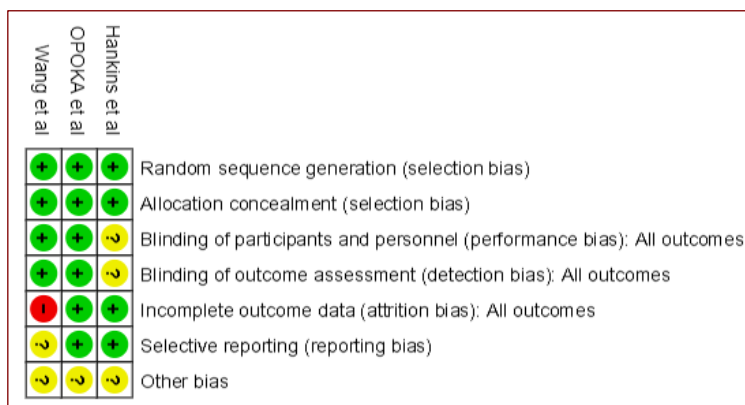


Figure 2. Study quality assessment based on Cochrane 5.2.0 risk of bias tools.

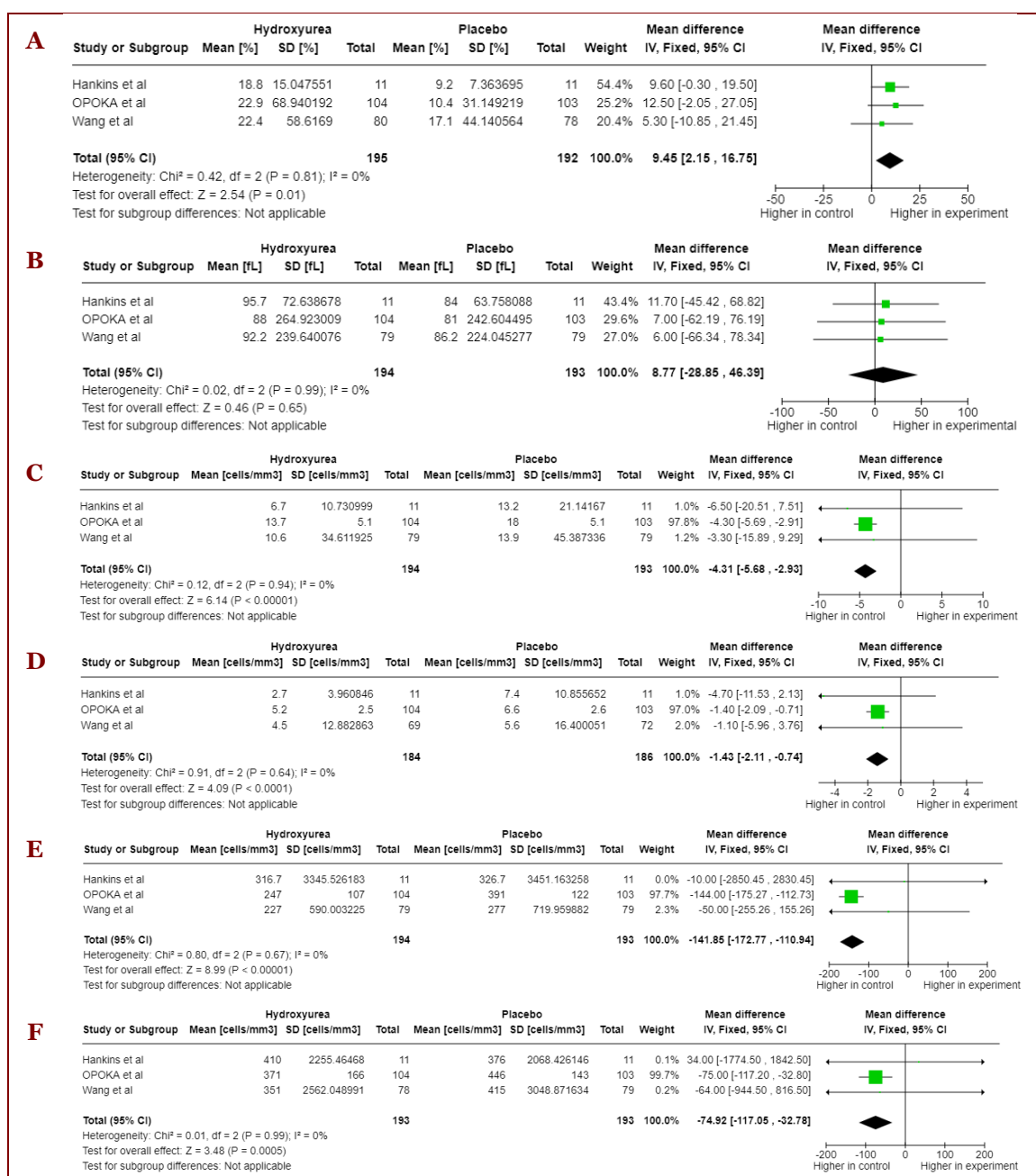


Figure 3. Effects of hydroxyurea on HbF (A), MCV (B), WBC (C), ANC (D), ARC (E), and platelet count (F). The pooled estimates were computed with random-effect model.

Effects on WBC, ANC, ARC, and platelet count

The effect of hydroxyurea on WBC was reported in three studies [27-29], where the pooled estimates are presented in **Figure 3C**. The effect was found to be significant ($p < 0.001$) with MD of -4.21 cells/mm³ (95%CI: -5.68 – -2.93). Similarly, the effect of hydroxyurea on ANC ($p < 0.001$), ARC ($p < 0.001$), and platelet count ($p < 0.001$) were significant with MDs of -1.43 cells/mm³ (95%CI: -2.11 – -0.74), -141.85 cells/mm³ (95%CI: -172.77 – -110.94), and -74.92 cells/mm³ (95%CI: -117.05 – -32.78), respectively. The I^2 values were 0% across all outcomes, suggesting the absence of heterogeneity in the pooled estimate.

Discussion

The findings from the present study revealed that hydroxyurea treatment is significantly effective in managing HbS, as indicated by the significant increase of HbF and reductions of WBC, ANC, ARC, and platelet count. Hydroxyurea functions as an antineoplastic agent by increasing HbF levels in patients with sickle cell anemia [16]. As suggested by an *in vivo* study, the primary mechanism of hydroxyurea is through the reversible inhibition of ribonucleotide reductase (RR) [30]. This mechanism disrupts cellular progression through the S phase of the cell cycle [31,32]. Optimal therapy for SCA involves promoting the production of HbF ($\alpha_2\gamma_2$), as well as its hybrid tetramer ($\alpha_2\beta\gamma$) [33]. Both play a crucial role in preventing the polymerization of sickle hemoglobin under deoxygenated conditions, thereby mitigating the cellular damage typically caused by deoxygenated sickle hemoglobin [34,35]. Daily hydroxyurea administration induces a temporary cessation of hematopoiesis, leading to altered erythroid kinetics during the recovery phase. This process, known as 'stress erythropoiesis,' involves the recruitment of early erythroid progenitors capable of producing HbF, resulting in elevated HbF levels [36,37]. In patients with sickle cell disease, hydroxyurea therapy has been shown to significantly increase HbF levels, ranging from 5 to 18 times above baseline [2,9]. Erythrocytes with higher HbF levels also exhibit increased MCV [38]. Notably, MCV was significantly lower in anemic patients compared to non-anemic ones, suggesting a direct relationship between increased HbF levels and cell volume [39].

Numerous studies have shown that leukocytes play a significant role in the progression of sickle hemoglobinopathies, with infections often triggering sickle cell crises and increasing morbidity and mortality [12,35,40]. Hydroxyurea therapy has been beneficial in managing SCD by reducing total WBC counts, although levels often remain above normal even after treatment, reflecting a substantial but incomplete reduction in chronic inflammation [41,42]. Additionally, hydroxyurea lowers neutrophil counts and reduces their adhesion to vascular endothelium, though this can lead to neutropenia [43]. A more comprehensive approach to managing SCD may involve targeting neutrophils to further reduce inflammation and related complications [44]. This study confirmed significant reductions in leucocyte and platelet counts after hydroxyurea therapy, which are known to trigger vaso-occlusive events [44]. In terms of its clinical use, the initial dosage of hydroxyurea recommended by the Food and Drug Administration of the United States for pediatric patients aged 2 years and older is 20 mg/kg per day [40]. In 2018, The Food and Drugs Authority of Ghana approved hydroxyurea for treating sickle cell disease in both adult and pediatric populations [45].

There are some limitations that are worth considering when interpreting the findings of this present study. The study included a relatively small sample size, with only three RCTs involving 423 participants. While exclusively included RCTs could reduce the heterogeneity, the systematic review excluded real-world or post-licensure studies, which dismiss valuable insights from observational studies that reflect the drug's performance in broader real-world settings. We did not estimate the treatment effects on other important parameters, such as quality of life and safety. Moreover, a significant number of potentially relevant studies were not included because their full texts were not retrievable. Further, the present study relied solely on database searches without performing a manual search of reference lists or other sources.

Conclusion

The addition of hydroxyurea to the standard of care of SCA could effectively improve the management results, as indicated by the increased HbF and reduced WBC, ANC, ARC, and

platelet count. The study supports the clinical use of hydroxyurea in managing SCA for pediatric patients. We recommend further randomized control study to be conducted covering all important parameters (such as blood parameters, quality of life, and adverse effects) on this specific population.

Ethics approval

Not required.

Acknowledgments

None to declare.

Competing interests

Authors have no known conflict of interest in relation to the publication of this work.

Funding

This study received no external funding.

Underlying data

No new data were generated in this study.

How to cite

Khansa F, Ghifari MH, Daffa MB, *et al.* Hydroxyurea therapy for children with sickle cell anemia: A systematic review and meta-analysis. *Narra X* 2024; 2 (2): e164 - <https://doi.org/10.52225/narrax.v2i2.164>.

References

1. Payne AB, Mehal JM, Chapman C, *et al.* Trends in sickle cell disease–related mortality in the United States, 1979 to 2017. *Ann Emerg Med* 2020;76(3):S28-S36.
2. Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: A review. *JAMA* 2022;328(1):57-68.
3. Kasztan M, Aban I, Baker K, *et al.* Natural history and variability in albuminuria in pediatric and murine sickle cell anemia. *Blood Advances* 2023;7(22):6850-6858.
4. Hammoudi N, Lionnet F, Redheuil A, Montalescot G. Cardiovascular manifestations of sickle cell disease. *Eur Heart J* 2020;41(13):1365-1373.
5. AlRyalat SA, Nawaiseh M, Aladwan B, *et al.* Ocular manifestations of sickle cell disease: Signs, symptoms and complications. *Ophthalmic Epidemiol* 2020;27(4):259-264.
6. Nancy A, Sukinah A, Maram A, *et al.* Dental and skeletal manifestation of sickle-cell anaemia and thalassemia in Saudi Arabia; A systematic Review. *IJPRAS* 2021;10(3-2021):1-7.
7. Dantas MT, Lopes A, Ladeia AMT. Association between lipid profile and clinical manifestations in sickle cell anemia: A systematic review. *Int J Cardiovasc Sci* 2022;35:770-779.
8. Pokhrel A, Olayemi A, Ogbonda S, *et al.* Racial and ethnic differences in sickle cell disease within the United States: From demographics to outcomes. *Eur J Haematol* 2023;110(5):554-563.
9. Steinberg MH. Fetal hemoglobin in sickle hemoglobinopathies: High HbF genotypes and phenotypes. *J Clin Med* 2020;9(11):3782.
10. Esoh K, Wonkam A. Evolutionary history of sickle-cell mutation: Implications for global genetic medicine. *Hum Mol Genet* 2021;30(R1):R119-R128.
11. Odame I, Jain D. Sickle cell disease: Progress made and challenges ahead. *Indian J Med Res* 2020;151(6):505-508.
12. Dua M, Bello-Manga H, Carroll YM, *et al.* Strategies to increase access to basic sickle cell disease care in low- and middle-income countries. *Expert Rev Hematol* 2022;15(4):333-344.
13. Karkoska K, Todd K, Niss O, *et al.* Implementation of near-universal hydroxyurea uptake among children with sickle cell anemia: A single-center experience. *Pediatr Blood Cancer* 2021;68(6):e29008.

14. Teigen D, Opoka RO, Kasirye P, *et al.* Cost-effectiveness of hydroxyurea for sickle cell anemia in a low-income African setting: A model-based evaluation of two dosing regimens. *Pharmacoeconomics* 2023;41(12):1603-1615.
15. Lee S, Vania DK, Bhor M, *et al.* Patient-reported outcomes and economic burden of adults with sickle cell disease in the United States: A systematic review. *Int J Gen Med* 2020;13:361-377.
16. Creary SE, Beeman C, Stanek J, *et al.* Impact of hydroxyurea dose and adherence on hematologic outcomes for children with sickle cell anemia. *Pediatr Blood Cancer* 2022;69(6):e29607.
17. Gupta N, Hiwale K, Vagha S, *et al.* Clinical outcome and laboratory parameters in sickle cell anemia patients of pediatric age group post hydroxyurea therapy. *J Pharm Res Int* 2021;33(63A):65-70.
18. Hashemi Z, Ebrahimzadeh MA. Hemoglobin F (HbF) inducers; history, structure and efficacies. *Mini Rev Med Chem* 2022;22(1):52-68.
19. Rankine-Mullings AE, Nevitt SJ. Hydroxyurea (hydroxycarbamide) for sickle cell disease. *Cochrane Database Syst Rev* 2022;9(9):CD002202.
20. Manoharan A, Enggist S. Hydroxyurea: An old drug in need of new clinical trials in myeloproliferative neoplasms. *Preprints* 2024;2024080323.
21. Reeves SL, Peng HK, Wing JJ, *et al.* Changes in hydroxyurea use among youths enrolled in Medicaid with sickle cell anemia after 2014 revision of clinical guidelines. *JAMA Netw Open* 2023;6(3):e234584-e234584.
22. Martimbianco ALC, Sá KMM, Santos GM, *et al.* Most Cochrane systematic reviews and protocols did not adhere to the Cochrane's risk of bias 2.0 tool. *Rev Assoc Med Bras* 2023;69(3):469-472.
23. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
24. Minozzi S, Cinquini M, Gianola S, *et al.* The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. *J Clin Epidemiol* 2020;126:37-44.
25. Migliavaca CB, Stein C, Colpani V, *et al.* Meta-analysis of prevalence: I^2 statistic and how to deal with heterogeneity. *Res Synth Methods* 2022;13(3):363-367.
26. Higgins JPT, Li T. Exploring heterogeneity. In: Egger M, Higgins JPT, Smith GD, editors. *Systematic reviews in health research: Meta-analysis in context*. New Jersey: John Wiley & Sons Ltd; 2022.
27. Wang WC, Ware RE, Miller ST, *et al.* Hydroxycarbamide in very young children with sickle-cell anaemia: A multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011;377(9778):1663-1672.
28. Hankins JS, McCarville MB, Rankine-Mullings A, *et al.* Prevention of conversion to abnormal transcranial Doppler with hydroxyurea in sickle cell anemia: AP hase III international randomized clinical trial. *Am J Hematol* 2015;90(12):1099-1105.
29. Opoka RO, Ndugwa CM, Latham TS, *et al.* Novel use of hydroxyurea in an African region with malaria (NOHARM): A trial for children with sickle cell anemia. *Blood* 2017;130(24):2585-2593.
30. Singh A, Xu Y-J. The cell killing mechanisms of hydroxyurea. *Genes* 2016;7(11):99.
31. Musiałek MW, Rybaczek D. Hydroxyurea—the good, the bad and the ugly. *Genes* 2021;12(7):1096.
32. Kapor S, Čokić V, Santibanez JF. Mechanisms of hydroxyurea-induced cellular senescence: An oxidative stress connection?. *Oxid Med Cell Longev* 2021;2021(1):7753857.
33. Kargutkar N, Sawant-Mulay M, Hariharan P, *et al.* Role of microRNA in hydroxyurea mediated HbF induction in sickle cell anaemia patients. *Sci Rep* 2023;13(1):369.
34. Steinberg MH. "Sickling" in vertebrates: Animal studies vs. sickle cell disease. *Blood Rev* 2019;36:88-94.
35. Henry ER, Metaferia B, Li Q, *et al.* Treatment of sickle cell disease by increasing oxygen affinity of hemoglobin. *Blood* 2021;138(13):1172-1181.
36. Walker AL, Crosby D, Miller V, *et al.* Hydroxyurea decouples persistent F-cell elevation and induction of γ -globin. *Exp Hematol* 2022;112-113:15-23.e1.
37. Huff SE, Winter JM, Dealwis CG. Inhibitors of the cancer target ribonucleotide reductase, past and present. *Biomolecules* 2022;12(6):815.
38. Jeremiah Z, Magnus A. Elevated mean cell volume in sickle cell anaemia: One story, too many? *Sanamed* 2024;19(1).
39. Arishi WA, Alhadrami HA, Zourob M. Techniques for the detection of sickle cell disease: A review. *Micromachines* 2021;12(5):519.
40. Archer N, Galacteros F, Brugnara C. 2015 Clinical trials update in sickle cell anemia. *Am J Hematol* 2015;90(10):934-950.

41. Zahran AM, Nafady A, Saad K, *et al.* Effect of hydroxyurea treatment on the inflammatory markers among children with sickle cell disease. *Clin Appl Thromb Hemost* 2020;26:1076029619895111.
42. Siriworadetkun S, Thientavor C, Thubthed R, *et al.* A comprehensive study of immune function and immunophenotyping of white blood cells from β -thalassaemia/HbE patients on hydroxyurea supports the safety of the drug. *Br J Haematol* 2023;200(3):367-376.
43. de Montalembert M, Voskaridou E, Oevermann L, *et al.* Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. *Am J Hematol* 2021;96(10):1223-1231.
44. Iqhrammullah M, Duta TF, Alina M, *et al.* Role of lowered level of serum vitamin D on diabetic foot ulcer and its possible pathomechanism: A systematic review, meta-analysis, and meta-regression. *Diabetes Epidemiol Manag* 2024;13:100175.
45. Allotey-Babington GL, Seaneke OA, Williams AA, *et al.* Hydroxyurea granules for the management of sickle cell disease in children. *Sci Afr* 2022;16:e01271.