REVIEW ARTICLE

Comprehensive Insights into Hydroxyurea Treatment for Children with Sickle Cell Disease: A Critical Review

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Abstract

Sickle cell disease (SCD) poses a significant global health challenge, affecting millions with unique implications for red blood cells and associated complications. This critical review, titled "Comprehensive Insights into Hydroxyurea (HU) therapy for Child with SCD," rigorously analyzes HU's safety and efficacy in pediatric SCD patients spanning 2000–2023. Employing meticulous methodologies, data synthesis involves diverse sources such as PubMed, Scopus, and the Cochrane Library, prioritizing relevance and research quality through structured title screening, abstract assessment, and full-text scrutiny. The review focuses on pediatric SCD, ensuring precision and applicability. Rigorous data extraction and specialized analyses assess occurrence rates across regions and populations, guiding clinical decisions and future research. Drawing insights from 14 distinct articles, the review provides a global perspective on HU treatment for pediatric SCD. Inclusive of diverse regions such as the USA, Saudi Arabia, Africa, Nigeria, India, Iran, and Yemen, it explores safety and efficacy across demographics. Varied study designs, including clinical trials, retrospective studies, and observational studies, contribute to a nuanced understanding of HU's impact. The age-diverse participant range and variable treatment durations enhance comprehensiveness. Consistently positive outcomes demonstrate HU's efficacy in pediatric SCD, showcasing reductions in crises, transfusions, and hospitalizations, alongside hematological improvements. With a well-established safety profile and minimal short-term adverse effects, HU emerges as a secure therapeutic option. Discussed studies from diverse regions highlight specific contributions to understanding HU therapy. Implications for clinical practice, research, and public health underscore the global need for wider HU availability. Future research should address long-term assessments, optimal dosage guidelines, personalized treatment approaches, and health-care utilization. Despite acknowledged limitations such as potential publication bias and methodological variations, this review, with its global perspective and comprehensive analysis, is a valuable resource for clinicians, researchers, and policymakers. Addressing identified limitations and exploring nuanced aspects are crucial for refining HU's role in managing pediatric SCD. In conclusion, "Comprehensive Insights into HU Treatment for Child with SCD" sheds light on HU therapy's multifaceted landscape across diverse studies. Synthesizing data from references articles, it provides a global perspective with consistent positive impacts on pediatric SCD, emphasizing reduced crises, hospitalizations, and transfusions, coupled with hematological improvements. Inclusion of varied study designs and patient cohorts enriches understanding. Despite limitations, this review is a valuable resource, urging further investigations to refine HU's role in managing pediatric SCD.

Key words: Clinical decisions, clinical practice, comprehensive analysis, evidence-based practices, future research, global perspective, hydroxyurea treatment, long-term assessments, optimal dosage guidelines, pediatric patients, personalized treatment, safety and efficacy, sickle cell disease

INTRODUCTION

Sickle cell disease (SCD), a global and potentially fatal hematologic disorder, presents a formidable health obstacle affecting millions worldwide. Marked by the abnormal sickle-shaped red blood cells (RBCs), this genetic condition triggers vaso-occlusion, disrupting blood flow in narrow vessels. This phenomenon leads to diminished blood supply, causing ischemia and inflammation in distant

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tissues. Acute painful sickle-cell crises serve as stark reminders of this process, emphasizing the urgent demand for impactful therapeutic interventions.[1] SCD, a prevalent hereditary blood disorder, is characterized by distinctive features within RBCs, setting it apart as a distinct health concern. Instead of the typical spherical shape, individuals with SCD exhibit crescent-shaped RBCs. This transformation arises from the conversion of hemoglobin (Hgb) into sickle hemoglobin (HgbS), triggered by a singular amino acid modification. Consequently, the modified Hgb induces blockages in blood vessels, leading to inflammation and a decrease in oxygen levels. The abnormal RBCs face premature removal from circulation, resulting in hemolytic anemia. The severity of the condition is closely tied to the presence of HgbS, with the onset of the disease marked by an elevation in HgbS levels in the body.[2] Sickle cell anemia (SCA), the most frequently encountered subtype of SCD, arises when an individual inherits two copies of the βs allele. Another prevalent variant is sickle cell Hgb disease, resulting from the concurrent presence of the βs and βc alleles. Furthermore, a common observation is HgbS/β-thalassemia, where β-thalassemia is inherited alongside the βs allele. The condition can also be linked to diverse genetic variations, including HgbS/D, HgbS/C, HgbS/O, and HgbS/A.[3] Sickle thalassemia and SCA stand out as prominent disorders in the spectrum of SCDs, both stemming from a singular genetic mutation. Inheritance occurs when an individual carries two HgbS genes, typically inherited from each parent, or when there is a combination of HgbS with other Hgb variants like β-thalassemia or HgbC. The severity of these conditions may be influenced by genetic modifiers such as α-thalassemia and fetal Hgb (HgbF) genes. α-thalassemia, characterized by the deletion of four α-globin genes, leads to reduced Hgb levels and exacerbates damage to erythrocytes.[4] Vaso-occlusion episodes in SCD cause tissue ischemia, which can cause acute and chronic discomfort in addition to possible harm to multiple organ systems, including the brain, lungs, kidneys, joints, spleen, and bones. According to the World Health Organization (WHO), between 300,000 and 500,000 children are born each year with severe hemoglobinopathy because 7% of the world's population contains Hgb mutation. There have been at least four cases of the independent formation of the HgbS mutation, with three of those occurrences occurring in sub-Saharan Africa and one in India or the Arabian Peninsula, especially in areas where malaria is a common disease. The sickle mutation, when present in a heterozygous state, offers defence against falciparum malaria and may even provide an advantage in survival. This mechanism is responsible for the mutation's persistently high incidence in particular populations found in sub-Saharan Africa, the Middle East, and India.[5,6] The projected annual births of infants affected by SCA are anticipated to reach around 400,000 by the year 2050. In sub-Saharan Africa, where challenges related to health infrastructure, nutrition, and prevalent infectious diseases such as malaria, tuberculosis, and HIV are widespread, the impact of the disease is further compounded. Affluent nations, representing <1% of the global disease burden, witness over 90% of infants with SCD surviving into adulthood, thanks to accessible newborn screening and comprehensive care facilities. In contrast, in low-income countries, these critical interventions are often inaccessible, resulting in up to 80% of individuals with SCD remaining undiagnosed, and less than half of them surviving beyond the age of 5.[7] As per the WHO, sickle cell disorder has a widespread impact, affecting around 275,000 individuals globally. Within this affected population, 56,000 individuals also grapple with thalassemia simultaneously. Among them, 30,000 require major transfusions as part of their medical treatment, and sadly, 5000 individuals succumb to the complications of SCD. In addition, another 1,000,000 individuals worldwide depend on regular transfusions as part of their ongoing medical care, resulting in 3000 fatalities annually associated with these interventions. These statistics highlight the substantial medical challenges and risks faced by individuals with sickle cell disorder, emphasizing the importance of medical interventions, despite the associated risks. The global incidence of SCD at birth is reported to be approximately 112 cases per 100,000 live births. Significantly, the incidence is higher in Africa, with 1125 cases per 100,000 live births. In contrast, Europe reports a lower incidence of 43.12 cases per 100,000 live births, highlighting regional variations in the prevalence of the disease. Mortality rates also vary globally, with the global average mortality rate at 0.64 per 100 child-years of observation, indicating the inherent risk of death associated with SCD. Africa reports the highest mortality rate at 7.3, underscoring the heightened challenges and health disparities faced by individuals with sickle cell disorder in this region. Overall, the data emphasizes the global impact of SCD, highlighting the critical need for an awareness, intervention, and support for affected individuals, particularly in regions with higher prevalence and associated mortality rates.[8] The sickle cell gene, first identified in the Nilgiri Hills in 1952, is prevalent in the Deccan plateau of central India, with smaller concentrations in northern Kerala and Tamil Nadu. The Anthropological Survey of India indicates that the sickle cell trait can reach up to 35% in specific communities. In India, SCD exhibits variations, with some individuals experiencing milder symptoms reminiscent of the Asian haplotype of SS disease. Cases in central India tend to be more severe, potentially influenced by the mode of patient identification, as hospitalized cases often present increased severity. The assumption that tribal populations are more susceptible to the HgbS gene is challenged by its widespread distribution among both tribal and non-tribal populations. Variances in clinical severity between tribal and non-tribal groups are noted, with some attributing milder disease in tribal populations to elevated alpha thalassemia frequencies. Recent research conducted at Akola Medical College in Maharashtra reveals a significant proportion of SCD patients exhibiting sickle cell-beta thalassemia, with prevalence differences in alpha thalassemia compared to other regions of India.[9] This underscores the nuanced nature of SCD in the Indian context, emphasizing the importance of region-specific considerations in understanding its prevalence and clinical manifestations. In India, the prevalence of the sickle gene varies widely, ranging from 2% to 34%. A study in central India, focusing on patients

over a period of up to 5.8 years, revealed that out of the participants, 96 individuals experienced severe manifestations of SCD. Significantly, among these patients, 74 were managed with the therapeutic use of hydroxyurea (HU). This information highlights the diversity in the prevalence of the sickle gene within the Indian population and underscores the significance of medical interventions, such as HU treatment, in addressing the severity of SCD in affected individuals.[10] The underlying mechanism of SCD centers on the formation of HgbS polymers under low oxygen levels, leading to structural changes in RBCs. SCD originates from a mutation in the β-globin gene, specifically altering the 17th nucleotide and amino acid in the β-globin chain. This genetic modification introduces a hydrophobic pattern in the deoxygenated HgbS tetramer, resulting in crystallization and polymerization. As a consequence, RBCs carrying HgbS with internal Hgb polymer become trapped in the microcirculation, causing vaso-occlusion. Vaso-occlusion, coupled with hemolytic anemia, contributes to complications affecting various organs. RBCs with HgbS undergo both intrinsic and extravascular hemolysis, leading to persistent anemia characterized by Hgb levels typically ranging from 6 to 11 g/dL.[11,12] The hemolysis hypothesis posits that the depletion of nitric oxide in the microcirculation is a consequence of intravascular hemolysis through a deoxygenation reaction.[13] In SCD, there is a reduction in plasma nitric oxide levels, accompanied by an elevation in endothelin-1 levels during vaso-occlusion. This shift from the normal equilibrium toward a constrictive state impedes blood flow, precipitating the onset of vaso-occlusion.[14] Vaso-occlusive crises, a distinctive hallmark of SCD, typically result from a complex interplay of factors including hypoxia, acidosis, inflammatory stress, and the activation of endothelial cells. These factors collectively contribute to the entrapment of sickle-shaped red and white blood cells in small blood vessels.[15] This process causes erythrocytes to lose their flexibility and shape, which leads to cellular dehydration and oxidative and physical stress. Intracellular HgbS concentration, the length of Hgb deoxygenation, and the presence of HgbF are some of the factors that affect the rate of HgbS polymerization. The rate of HgbS polymerization and genetic variables such as α-thalassemia or hereditary persistence of HgbF affect the severity of the disease. Hemolytic anemia and ischemia-reperfusion damage are associated with vaso-occlusion in the pathogenesis of SCD. Vaso-occlusive pain is brought on by inflammatory vascular blockage brought on by cells becoming trapped in the microcirculation. Due to HgbS polymerization, hemolytic anemia can lead to vasculopathy, which includes endothelial dysfunction and hypertension. Free plasma Hgb is released during hemolysis, which causes the production of reactive oxygen species, nitric oxide resistance, and hypercoagulability. This condition could be exacerbated by arginine and nitric oxide depletion over time. The pathophysiology of SCD is further complicated by the discharge of erythrocyte microvesicles carrying tissue factor.[3] This multifaceted understanding illuminates the intricate processes underlying the development and progression of SCD. Clinical challenges arise from the wide range of manifestations of SCD. Acute exacerbation of anemia (hyperhemolysis, acute splenic sequestration, and aplastic crises), cardiac complications (cardiomyopathy, cardiomegaly, and congestive heart failure), disruptions of growth and development, and cardiac complications are among the most common manifestations of SCD. Hepatic sequestration and intrahepatic cholestasis are examples of complications related to the digestive system and hepatobiliary system. Neurologic complications include cerebrovascular accident and silent cerebral infarct. Ophthalmologic complications include cataract disease, proliferative sickle retinopathy, vitreous hemorrhage, and retinal detachment. Pain syndromes include vacuum-occlusive episodes. Pulmonary complications include acute chest syndrome (ACS) and pulmonary hypertension. Renal and genitourinary complications include priapism and skeletal and skin complications. Finally, transfusion and iron overload are related to the immune system and hemosiderosis.[16] This comprehensive list underscores the multi-systemic impact of SCD, emphasizing the need for a holistic approach to its management and care. Preventive penicillin therapy has demonstrated efficacy in mitigating the occurrence of pneumococcal illness in children below the age of five. In addition, individuals with SCD require essential folate supplementation due to the shorter lifespan (12–16 days) of their sickled RBCs. This increased cell turnover necessitates higher erythropoiesis, elevating the risk of folate deficiency.[17] To prevent life-threatening complications, the transfusion of RBCs stands as a crucial intervention. This entails administering regular transfusions at predetermined intervals to sustain appropriate levels of HgbS.[18] The prevention of cellular adhesion is accomplished through the use of medications such as crizanlizumab, a humanized monoclonal antibody, and rivipansel, a synthetic glycomimetic inhibitor.[19] While the potential for utilizing gene therapy in the management of SCD exists, additional scientific and clinical exploration is needed.[20] Leg ulcers, impacting 5–10% of patients, are a prevalent problem, and their management may involve the use of narcotic analgesics and corporeal body irrigation.[21] The use of antioxidant therapy, incorporating substances such as omega-3 fatty acids and N-acetylcysteine, holds promise in impeding dense cell formation and replenishing glutathione levels.[22] This multifaceted approach highlights the diverse strategies employed in the comprehensive management of SCD, addressing both preventive measures and therapeutic interventions. HU is the preferred therapeutic choice in the treatment of SCD, exerting its effects through the reduction of platelet and neutrophil counts. This mechanism contributes to the alleviation of cell adhesion, attenuation of inflammation pathways, and augmentation of nitric oxide levels associated with hemolysis in SCD.[17] Initially used to elevate HbF levels in individuals with SCA, HU's manifold benefits, particularly when initiated early, extend to mitigating childhood organ damage and reducing susceptibility to injuries related to SCD in the brain, spleen, and kidneys.[23] Hydroxycarbamide, a derivative of HU, fosters an increase in HgbF levels and impedes the polymerization of HgbS, resulting in a reduction in painful crises and hospitalizations associated

with SCD.[24] It affects both early and erythroid progenitors, resulting in increased HgbF levels and raised γ-globulin and Hgb mRNA levels.[3] Since HU can be hematologically hazardous, it is usually advised for patients who have three or more vaso-occlusive events per year along with a history of ACS, chronic anemia, and ongoing pain. Vigilant supervision is necessary for vital metrics such as platelet, neutrophil, reticulocyte, and erythrocyte levels.[25,26] Despite its effectiveness, HU's primary side effect is myelosuppression, with reported instances of aplasia lasting from weeks to months. Concerns also exist regarding the potential development of malignancies, particularly leukemia, although further research is needed to ascertain the exact risk. While the use of HU in SCD has shown a modifying response in some children, its efficacy remains unclear in others. As the role of HU in SCD treatment is evolving, comprehensive clinical trials are imperative for a thorough understanding of its effectiveness. Common side effects associated with HU encompass myelosuppression, hyperpigmentation, organ damage, nausea, rash, and leg ulcers. The long-term effectiveness of HU in preventing recurrent vaso-occlusive episodes in SCD is not clearly defined. It is noteworthy that patients undergoing HU treatment may experience episodes of low blood counts due to myelosuppression, and the medication has also been shown to increase nitric oxide production as a result of intravascular hemolysis.[27,28]

Significance of study

The critical review titled "Comprehensive Insights into HU Treatment for Children with SCD" holds paramount importance in pediatric health care, providing a consolidated and in-depth analysis of HU treatment for SCD. It is important because it directs clinical decision-making for medical professionals, allowing them to create individualized treatment regimens for children with SCD based on a comprehensive knowledge of the potential adverse reactions and effectiveness of HU. By offering comprehensive insights, the study directly contributes to improved patient outcomes, potentially reducing the severity and frequency of vaso-occlusive episodes and enhancing the overall health-related quality of life for pediatric patients. Furthermore, the review informs therapeutic strategies, empowering researchers and clinicians to refine protocols and explore innovative treatment approaches. It serves as a valuable resource for parents and caregivers, fostering better communication with health-care providers and promoting informed decision-making. In addition, the study's findings can influence health-care policies and guidelines, supporting evidence-based practices in the management of pediatric SCD, while also directing future research endeavors to address existing knowledge gaps.

Rationale of the study

SCD poses a significant health-related challenge, particularly in pediatric populations, necessitating a thorough evaluation of available treatment options. HU has emerged as a promising therapeutic intervention, but a comprehensive and critical examination of its safety and efficacy across diverse studies is essential. The rationale for this critical review lies in the need to consolidate, analyze, and critically assess a wealth of evidence from various studies to provide a nuanced understanding of HU's impact on pediatric patients with SCD. By critically evaluating the available literature, we aim to offer insights into the effectiveness, safety profile, and potential challenges associated with HU treatment, ultimately guiding clinicians, researchers, and policymakers in optimizing SCD management strategies.

Purpose of the study

The prime purpose of this critical review is to synthesize data and critically analyze existing literature on HU treatment in pediatric SCD patients. The review seeks to provide a comprehensive understanding of the varied impacts of HU, including its efficacy in reducing vaso-occlusive crises, improving hematological parameters, and its safety profile in diverse demographic settings. The study also seeks to highlight knowledge gaps, suggest possible directions for future studies, and provide useful advice for medical professionals who treat young patients with SCD. By critically examining the evidence, our goal is to contribute to the refinement of treatment protocols, promote evidence-based decision-making, and enhance the overall quality of care for children grappling with this challenging hematological condition.

Need of the study

The need for a comprehensive review on HU treatment for children with SCD stems from the significant impact of this condition on affected individuals. SCD, characterized by abnormal Hgb and distorted RBCs, poses substantial health challenges, particularly in children. The utilization of HU has emerged as a promising therapeutic avenue, showing potential in mitigating the severity of symptoms and improving overall health-related quality of life. However, a thorough understanding of its mechanisms, efficacy, and potential implications for pediatric patients is crucial. This critical review aims to address the existing knowledge gaps surrounding HU treatment in the context of pediatric SCD. By synthesizing available literature and research findings, the study seeks to provide comprehensive insights into the treatment's mechanisms of action, its effectiveness in managing the disease, and potential considerations for its use in pediatric populations. Understanding the nuances of HU treatment is essential for health-care practitioners, researchers, and policymakers involved in the care and management of children with SCD. Furthermore, as advancements in medical research and technology continue to evolve, an up-to-date and critical review will contribute to the current body of knowledge, assisting in the refinement of treatment protocols and the development of

future therapeutic strategies. Ultimately, the study's findings may have implications for improving clinical outcomes, enhancing the health-related quality of life for pediatric patients with SCD, and guiding future research directions in the field.

METHODOLOGY

Search strategy

Search strategy used in the search of bibliographic databases: To develop an effective search strategy for a systematic review titled "Comprehensive Insights into HU Treatment for Children with Sickle Cell Disease: A Critical Review," it is essential to follow a structured approach. Begin by defining key concepts: "Hydroxyurea," "Children," and "Sickle Cell Disease." Next, identify keywords and their synonyms, such as HU (hydroxycarbamide), children (pediatric, child, adolescent), and (SCD, Hgb SS, hemoglobinopathies). Combine these terms using Boolean operators, employing AND to link different concepts (HU AND children AND SCD) and OR to incorporate synonyms ((HU OR hydroxycarbamide) AND (children OR pediatric OR adolescent) AND (SCD OR hemoglobinopathies)). This critical review titled "Comprehensive Insights into HU Treatment for Children with SCD," rigorously explores the safety and effectiveness of HU in pediatric patients diagnosed with SCD from 2000 to 2023. Employing an exhaustive search strategy, the study delves into databases such as PubMed, Scopus, and authoritative repositories like the Cochrane Library. The objective is to provide a contemporary and thorough evaluation of HU's impact on pediatric SCD treatment by synthesizing information from diverse and reputable sources. The meticulous methodology involves systematic searches of relevant literature, including research articles and clinical studies, focusing on children with SCD. Through this approach, the review aims to extract meaningful data, draw evidence-based conclusions, and contribute valuable insights to inform clinical practices and guide future research in the field.

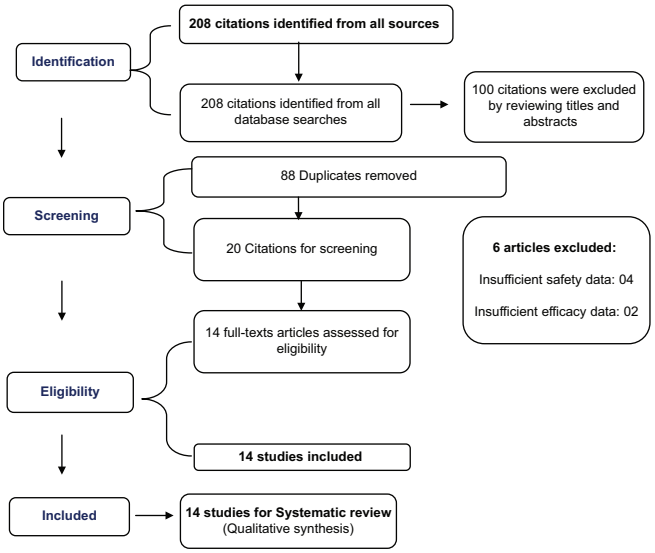
Selection process

The selection process for this review begins with a meticulous screening of titles and abstracts to identify articles and studies specifically addressing "Comprehensive Insights into HU Treatment for Childwith SCD." Subsequently, a detailed review of full-text articles is conducted, applying stringent inclusion criteria that prioritize relevance and research quality. Various study types, such as clinical trials, observational investigations, and systematic reviews, are considered, with a specific focus on pediatric patients diagnosed with SCD. An intentional exclusion of articles behind paywalls ensures the incorporation of openly available data sources, enhancing accessibility and transparency. Through this thorough selection process, the goal is to compile a robust and pertinent body of evidence, facilitating a comprehensive examination of HU's impact on the pediatric SCD population.

Data compilation

The process of compiling data for comprehensive insights into HU treatment for child with SCD involves systematic extraction from studies that meet the inclusion criteria. A structured data extraction form is utilized to maintain accuracy and consistency, capturing essential data points from the selected studies. The adherence to a pre-defined checklist enhances transparency and rigor, which is vital for assembling a comprehensive and reliable dataset. This meticulous approach to data compilation strengthens the study's capacity to offer an in-depth analysis of HU's safety and effectiveness in the context of pediatric SCD.

Flowchart of results of search strategy



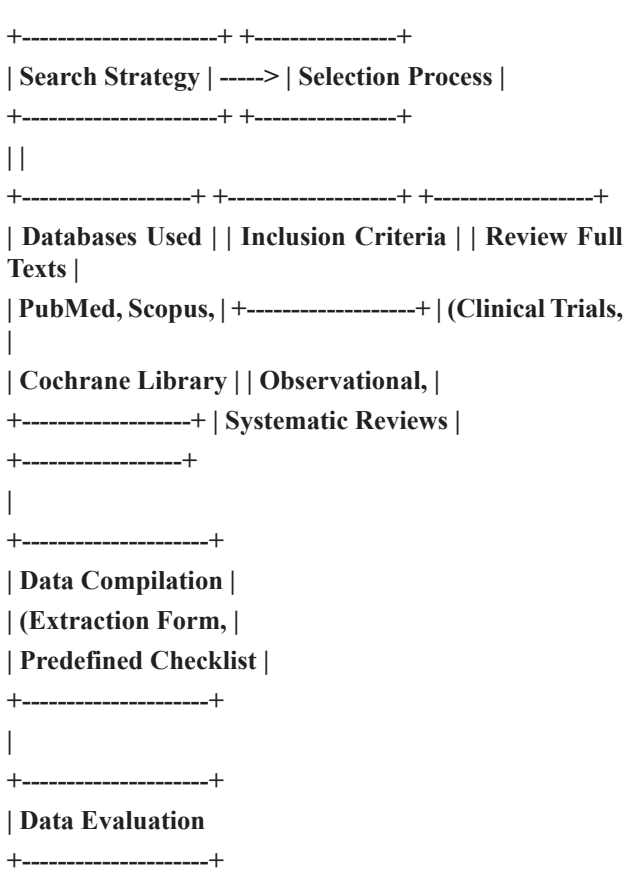
Data evaluation

The data evaluation process encompasses a thorough examination of aggregate occurrence rates pertinent to comprehensive insights into HU treatment for children with SCD. Specialized analyses are employed to assess the frequency of key factors within the specific cohort of pediatric patients with SCD, ensuring comprehensive coverage across varied regions and populations. Utilizing quantitative values derived from meticulously extracted information enables the synthesis and consolidation of findings, contributing to a holistic and nuanced assessment of HU's safety and efficacy in the realm of pediatric SCD. This approach is designed to facilitate a profound and well-informed analysis of the treatment's impact on the target population.

The role of a co-author in the systematic review "Comprehensive Insights into HU Treatment for Children

with Sickle Cell Disease: A Critical Review" encompasses several key responsibilities. The co-author collaborates in defining key concepts and identifying relevant keywords, ensuring comprehensive coverage of the topic. They actively refine the search strategy, using Boolean operators and synonyms to optimize the search. The co-author conducts searches across major databases such as PubMed, Scopus, Web of Science, and the Cochrane Library to gather relevant studies. During the data evaluation phase, they meticulously examine aggregate occurrence rates and perform specialized analyses on the pediatric SCD cohort. In addition, the co-author synthesizes and consolidates findings to provide a nuanced understanding of HU's safety and efficacy. They also document the entire search strategy, including search terms, databases searched, results obtained, and any limits applied, ensuring the review process is reproducible and transparent.

Flow Chart



RESULTS

This comprehensive report synthesizes findings from an extensive dataset of 108 references, meticulously curated through electronic database searches and article bibliography reviews. After eliminating duplicates, 14 distinct articles were identified, each significantly contributing to understanding HU's safety and effectiveness in pediatric patients with SCD. The studies, conducted across diverse countries including the USA, Saudi Arabia, Africa, Nigeria, India, Iran, and Yemen, aimed to provide a thorough understanding of HU's impact on various aspects of SCD management. HU, L-glutamine, and crizanlizumab are essential treatments for SCD, each offering unique benefits and limitations in efficacy and safety. HU is well established for reducing painful episodes by increasing HgbF but requires regular monitoring due to side effects like myelosuppression. L-glutamine, approved more recently, reduces oxidative stress within sickle cells and is generally safe, enhancing therapeutic effects when combined with other treatments. Crizanlizumab targets adhesion molecules to decrease vaso-occlusive episodes, effectively reducing pain and being well-tolerated by patients. The choice among these treatments depends on individual patient profiles and disease severity, with HU being the most studied, while L-glutamine and crizanlizumab provide promising alternatives with fewer side effects.

The characteristics of study designs encompass a diverse range of research methodologies, reflecting the multifaceted nature of investigating HU's effects. Clinical trials, retrospective studies, double-blind randomized trials, and observational studies were included. This methodological diversity enhances the robustness of the findings, covering a broad spectrum of research perspectives.

The age range of participants in the reviewed studies spans from infancy to 21 years, ensuring a comprehensive representation of pediatric and adolescent populations. The diverse demographic characteristics contribute to a holistic understanding of HU's applicability across varied patient profiles. The studies varied in duration, from 6 months to an extensive 27 years, providing insights into both short-term and long-term implications of HU treatment.

Dosage regimens ranged from 10 mg/kg/day to 35 mg/kg/day, showing the versatility and adaptability of HU administration. Positive results, such as a decrease in blood transfusions, ACS episodes, vaso-occlusive crises, and hospital stays, are regularly demonstrated by key data. Hgb levels, HgbF percentages, and other hematological measures that show improvements highlight the drug's ability to modify the condition. With few short-term side effects and a well-established safety profile, HU is positioned as a secure treatment option for kids with SCD.

To summarize, this comprehensive report presents a global perspective on the safety and effectiveness of HU treatment in child patients with SCD. The consistent positive outcomes, coupled with the drug's favorable safety profile, position HU as a cornerstone in the comprehensive management of pediatric SCD. Ongoing research is crucial for refining dosage strategies, assessing long-term effects, and optimizing HU use in diverse pediatric populations with SCD, contributing to improved clinical outcomes and the overall quality of life for affected children. This synthesis contributes valuable insights to medical literature, informing clinicians and

Table 1: Safety and efficacy data of HU in pediatric SCD

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Hoppe *et al.*[29]	Journal of pediatric hematology/ oncology	Pilot Study	USA	8	2–5 years	--	137 Weeks	Positive results were found in the trial, as HU medication increased the levels of Hgb in both the fetal and total blood. Furthermore, during the course of HU treatment, the study found a decrease in hospital admission rates as well as in total hospital days. Remarkably, there were no unanticipated toxicity reports, and the subjects' growth and development continued as before.	The results of this pilot trial demonstrate that HU has the potential to be a therapeutic option for children with SCD because it is safe and effective in treating the condition.
Al Hawsawi *et al.*[30]	Journal of Taibah University Medical Sciences.	Retrospective Study	Saudi Arabia	10	5–15 years	15–30 mg/ kg/day	2 year	The outcomes of the study revealed a significant reduction in the frequency of painful crises and ACS episodes following HU treatment. Laboratory investigations further indicated a noteworthy increase in MCV and HgbF values after the administration of HU.	In summary, the study concludes that HU demonstrates effectiveness in managing SCD in children without major short-term adverse effects. However, the authors emphasize the necessity of long-term follow-up to assess potential adverse effects over an extended period. This underlines the importance of ongoing research to comprehensively evaluate the safety and efficacy of HU in the long run.

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Tshilolo *et al.*[31]	New England Journal of Medicine	Prospective Multicentric Study	Africa	635	1–10 years	15–20 mg/kg/day	6 months	The study reported a robust 94.2% retention rate at the 3-year mark, coupled with significant increases in Hgb and HgbF levels. Dose-limiting toxic events were minimal at 5.1%, falling below safety thresholds. During treatment, the incidence of dose-limiting toxic effects was 20.6 events per 100 patient-years, slightly lower than the pre-treatment rate of 20.7 events per 100 patient-years. HU therapy showcased noteworthy reductions in clinical adverse events: vaso-occlusive pain (98.3 vs. 44.6 events per 100 patient-years), nonmalaria infection (142.5 vs. 90.0 events per 100 patient-years), malaria (46.9 vs. 22.9 events per 100 patient-years), transfusions (43.3 vs. 14.2 events per 100 patient-years), and death (3.6 vs. 1.1 deaths per 100 patient-years).	The findings suggest that HU treatment is both feasible and safe in children with sickle cell anemia in sub-Saharan Africa. The observed reduction in vaso-occlusive events, infections, malaria, transfusions, and mortality emphasizes the importance of expanding access to HU treatment in this population.
Abdullahi *et al.*[32]	Blood	RCT	Nigeria	101	1–16 year	20 mg/kg/day	3 years	Results revealed 6 recurrent strokes and 2 deaths in the low-dose group, and 5 recurrent strokes and 3 deaths	

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
								in the moderate-dose group. The IRR for the primary outcome measure in both groups was 0.98 (95% confidence interval [CI], 0.32–3.00; *P*=0.97). The incidence rates of recurrent strokes were 7.1 and 6.0 per 100 person-years in the low- and moderate-dose groups, respectively, with an IRR of 1.18 (95% CI, 0.30–4.88; *P*=0.74). As an indicator of adherence to oral HU therapy, the median percentage of returned pills was 3.0% and 2.6% in the low- and moderate-dose groups, respectively. Importantly, no participant had HU therapy discontinued due to myelosuppression.	The study concluded that for children with sickle cell anemia in low-income settings without access to regular blood transfusion therapy, initial low-dose HU appears to be a minimally effective dose for secondary stroke prevention.
Reddy *et al.*[33]	Annals medicus	Retrospective Review	USA	113	1–18 year	35 mg/kg/day	5 year	The study revealed that young adults exhibited significantly higher HU adherence compared to adolescents and children. This was reflected in higher median HgbF percentage (HgbF%) (24.2 vs. 12.4 vs. 8.6, *P*=0.003), MCV (106.4 vs. 96.2 vs. 95.4, *P*=0.01), and lower ANC (3.25 vs. 4.9 vs. 4.2, *P*=0.01),	The findings emphasize that young adults with SCD tend to have better

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
								respectively. Patients experiencing chronic pain demonstrated lower HU adherence (HgbF% 15.3 vs. 10.7, *P*=0.04; ANC 3.6 vs. 6.3, *P*=0.002; MCV 102.3 vs. 93.1, *P*=0.1). Further analysis revealed that patients with higher HgbF or MCV and lower ANC had significantly fewer emergency room visits, hospitalizations, and shorter length of stays. These trends were consistent in the subgroup analysis focusing only on HgbSS patients. The study found no significant association between HU adherence and patients' sex, socio-economic status, distance from the hospital, and duration of HU treatment.	HU adherence compared to their younger counterparts. In addition, patients with lower HU adherence and chronic pain showed increased health-care utilization. The study underscores the importance of further research to identify barriers to adherence and develop interventions to optimize HU adherence in individuals with SCD.
Ofakunrin *et al.*[34]	Journal of Tropical Paediatrics	Quasi-experimental study	Nigeria	54	4–17 years Male: 30 Female: 24	29.7±5.1 mg/kg	12 month	The findings indicated that HU was effective in reducing vaso-occlusive crises, ACS, blood transfusions, hospitalizations, and the duration of hospital stays. Notably, there was a substantial 46.3% decrease in painful crises. The study also observed a decrease in leukocyte and	This research contributes to the growing

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
								platelet counts. While leukopenia occurred in 2 subjects at a 25 mg/kg dose, overall, HU was deemed safe and effective.	body of evidence supporting the efficacy and safety of HU in the management of SCD, particularly in reducing various complications and improving overall patient outcomes.
Jain *et al*.[35]	International Journal of Hgb Research	Double-blind randomised controlled trial	India	60	18 months	10 mg/kg/day	5–18 years Male: 28 Female: 32	The results revealed that HgbF levels and overall Hgb increased, and there was a notable decrease in painful crises, blood transfusions, and hospitalizations. The study also reported several adverse events. Overall, the findings support the effectiveness of a modest, fixed dose of HU in the treatment of individuals with SCD.	This study contributes valuable insights into the positive impact of HU in managing SCD, providing evidence for its efficacy in improving key hematological parameters and reducing the frequency of painful crises and associated complications.
Patel *et al*.[36]	International Journal of Hgb Research	Observational Study	India	27	3–14 years Male: 18 Female: 9	10 mg/kg/day	2 years	The results demonstrated a substantial 71.5% reduction in painful crises with HU therapy. In addition, baseline levels of HgbF, Hgb, MCV, and MCHC were increased. The study highlighted the positive impact of HU in improving both clinical and hematological parameters, underscoring its effectiveness even at a minimal dose of 10 mg/kg/day.	This research provides valuable evidence supporting the use of HU in the management of SCD, showcasing its potential to reduce painful crises and enhance key hematological indicators, even at lower doses.

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Meier *et al.*[37]	BMC	Randomised Multicenter Trials	USA	116	0.5–21 years	20 mg/kg/day	12 months	The findings underscored the disease-modifying effects of HU in sickle cell anemia. The study highlighted the significance of the HU dosage strategy and the age at which it is initiated in reducing complications associated with sickle cell anemia.	This research contributes valuable insights into the potential benefits of HU as a disease-modifying treatment, emphasizing the importance of tailored dosage strategies and timely initiation for optimal outcomes in individuals with sickle cell anemia.
Lobo *et al.*[38]	British Journal of Haematology	Retrospective Study	USA	267	3–18 years	20.8 mg/kg/day	2 years	The results indicated a significantly higher survival rate among HU -treated patients compared to untreated ones, primarily attributed to fewer deaths from ACS and infections. Although HU was associated with a decrease in Hgb concentration, HgbF, MCV, platelet count, and neutrophils, the study highlighted that it led to a reduction in the severity of the disease and a decrease in morbidity among children with SCD. The findings highlighted the positive impact of HU, revealing a decrease in the rate of hospitalization, transfusion	This research underscores the positive impact of HU therapy in improving the survival and overall well-being of children with SCD, emphasizing its potential to decrease the severity of the condition and mitigate associated health risks.

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Keikhaei *et al.*[39]	Global Journal of Health Science	Cohort Study	Iran	48	6–18 years Male: 24 Female: 24	10 mg/kg/day	1 year	requirements, and spleen size, along with an increase in Hgb, red blood cell (RBC) count, and HgbF levels in individuals with SCD. Importantly, the study noted a significant rise in HgbF, total Hgb, and RBC indices without any reported side effects, emphasizing the safety and efficacy of HU in this cohort.	This research contributes valuable evidence supporting the benefits of HU in improving various clinical parameters and overall outcomes in individuals with SCD, particularly in terms of reducing complications and enhancing hematological profiles.
Deshpande *et al.*[40]	Indian Journal of Haematology and Blood Transfusion	Single-Centre Clinical Trial	India	10	0–10 years	15–30 mg/kg/day	6–12 months	The results of the trial revealed positive outcomes associated with HU treatment, including an increase in HgbF, lower neutrophil and reticulocyte counts, and decreased adhesiveness and hemolysis. Importantly, the study concluded that HU is effective in reducing sickle cell crises and transfusion requirements, thereby enhancing the overall quality of life for patients with SCD	This research adds to the growing body of evidence supporting the effectiveness of HU in managing SCD, emphasizing its role in improving hematological parameters and alleviating clinical complications, ultimately contributing to an improved quality of life for affected individuals.
Reeves *et al.*[41]	Clinical paediatrics	Retrospective Study	USA	4435	1–17 years Male: 52% Female: 48%	--	2 years	The study observed that HU usage resulted in a notable decrease in various types of medical visits for children	This research underscores the importance

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
								across different age groups compared to non-users. In addition, the research indicated that the earlier initiation of HU correlated with a reduction in pain over the lifespan of a child. However, the study also identified a low prevalence of HU use in children, highlighting the need for interventions to increase both the utilization and adherence to HU therapy.	of promoting and optimizing HU treatment in pediatric patients to enhance health-care outcomes and alleviate pain associated with SCD.
Di Maggio *et al.*[42]	International Journal of Molecular Sciences	Prospective Study	Yemen	30	2–12.5 years	15 mg/kg/day	4 years	The findings indicated that HU administration resulted in a significant decrease in vaso-occlusive crises, blood transfusions, hospitalizations, ACS, and cerebrovascular strokes. In addition, the study observed an increase in Hgb levels and HgbF percentage. The research concluded that low-dose HU was found to be effective in Yemeni children with sickle cell anemia.	This study contributes valuable evidence supporting the efficacy of HU in managing sickle cell anemia in a Yemeni population, emphasizing its positive impact on clinical outcomes and hematological parameters.

HU: Hydroxyurea, SCD: Sickle cell disease, Hgb: Hemoglobin, HgbF: Fetal hemoglobin, ACS: Acute chest syndrome, MCV: Mean corpuscular volume, IRR: Incidence rate ratio, ANC: Absolute neutrophil count, MCHC: Mean corpuscular hemoglobin concentration

researchers alike on the evolving landscape of HU therapy in pediatric SCD management.

DISCUSSION

In this exhaustive exploration, our study meticulously curated a comprehensive dataset comprising 108 references, employing rigorous electronic database searches and meticulous reviews of article bibliographies. The elimination of duplicates resulted in the inclusion of 14 distinct articles, each playing a significant role in unraveling the intricacies of HU's safety and efficacy in pediatric patients with SCD. The geographical diversity of the studies, spanning the USA, Saudi Arabia, Africa, Nigeria, India, Iran, and Yemen, reflects our commitment to offering a global perspective on HU's impact across different regions. The overarching objective was to contribute to a nuanced understanding of HU's multifaceted influence on various facets of SCD management, consolidating evidence from diverse cultural and clinical contexts.

The pilot study conducted by Hoppe *et al*. provides valuable insights into the use of HU as a therapeutic option for pediatric patients with SCD. The trial's favorable results add to the increasing amount of data demonstrating HU's safety and effectiveness in this particular patient population. One striking discovery is the increase in Hgb levels, both in the fetal and total blood, indicating a positive impact on RBC synthesis. In addition, the decrease in hospital admission rates and total hospital days during HU treatment is a significant clinical outcome, suggesting the potential of HU in reducing the severity of SCD-related complications. The absence of unanticipated toxicity reports is particularly reassuring, emphasizing the safety profile of HU in the studied age group (2–5 years). Furthermore, the maintenance of subjects' growth and development throughout the trial period underscores the overall well-tolerated nature of HU. These findings collectively support the conclusion that HU holds promise as a safe and effective therapeutic option for children with SCD, warranting further investigation and consideration in broader clinical contexts. The results of this pilot study lay a foundation for future research and clinical practice in the clinical management of pediatric SCD.[29]

The retrospective study carried out in Saudi Arabia by Al Hawsawi *et al*. offers important new information about the safety and effectiveness of HU treatment in young SCD patients. The incidence of painful crises and episodes of ACS that were observed to decrease after the administration of HU highlights the medication's therapeutic potential in the management of problems connected to SCD. The significant rise in HgbF and mean corpuscular volume (MCV) values points to a beneficial effect on hematological parameters, which supports the notion that HU has disease-modifying properties. The study's conclusion that HU is effective in managing SCD in children without major short-term adverse effects is consistent with existing literature. However, the authors rightly emphasize the necessity of long-term follow-up to assess potential adverse effects over an extended period. This is a crucial consideration, as the long-term safety profile of HU is paramount for its sustained use in pediatric patients with SCD. The call for ongoing research to comprehensively evaluate the safety and effectiveness of HU aligns with the broader scientific goal of ensuring evidence-based and informed clinical practices. Overall, this study contributes to the understanding of HU's role in pediatric SCD management, emphasizing both its immediate benefits and the need for sustained vigilance through long-term monitoring.[30]

The prospective multicentric study conducted by Tshilolo *et al*. in Africa represents a significant contribution to the understanding of HU treatment in pediatric patients with SCA. The robust 94.2% retention rate at the 3-year mark highlights the feasibility of long-term HU therapy in this population. Furthermore, the study reports substantial increases in Hgb and HgbF levels, indicating the positive impact of HU on RBC production and the modulation of sickling episodes. The minimal dose-limiting toxic events at 5.1%, falling below safety thresholds, and the lower incidence of dose-limiting toxic effects during treatment compared to pre-treatment rates underscore the drug's safety profile in this setting. The significant reductions in vaso-occlusive pain, non-malaria infection, malaria, transfusions, and mortality associated with HU therapy demonstrate its efficacy in mitigating a wide range of clinical adverse events. The findings suggest that HU treatment is both feasible and safe in child with SCA in sub-Saharan Africa. The observed reductions in vaso-occlusive events, malaria, transfusions, infections, and mortality emphasize the potential benefits of expanding access to HU treatment in this population. The study provides valuable evidence supporting the inclusion of HU as a viable therapeutic option for pediatric patients with SCA in sub-Saharan Africa, contributing to the global knowledge base on the safety and efficacy of this intervention in diverse settings.[31]

The randomized controlled trial conducted by Abdullahi *et al*. in Nigeria, involving 101 participants aged 1–16 years over a 3-year period, aimed to assess the efficacy of low-dose HU in secondary to stroke prevention for child with SCA in low-income settings without regular blood transfusion therapy access. The results indicated that both the low-dose and moderate-dose groups showed similar incidence rates of recurrent strokes, with no significant difference in the primary outcome measure. Adherence to oral HU therapy, measured by the median percentage of returned pills, was comparable between the two groups, and no participant had therapy discontinued due to myelosuppression. While the study suggests that initial low-dose HU may be minimally effective for secondary stroke prevention in such settings, the findings underscore the need for further research and exploration of alternative strategies to enhance therapeutic

outcomes in this vulnerable population.[32]

The retrospective review conducted by Reddy *et al*. in the USA, involving 113 participants aged 1–18 years over a 5-year period, provides valuable insights into HU adherence patterns and their implications in the pediatric SCD population. Notably, the study reveals a significant association between age groups and HU adherence, with young adults exhibiting higher adherence compared to adolescents and children. This adherence pattern is further reflected in improved hematological parameters, including higher median HgbF percentage, MCV, and lower absolute neutrophil count. Conversely, patients experiencing chronic pain demonstrated lower HU adherence and associated adverse outcomes, such as increased health-care utilization. The study's comprehensive analysis also highlights the impact of HU adherence on emergency room visits, hospitalizations, and length of stays. Importantly, the findings underscore the need for further research to identify barriers to adherence and develop targeted interventions to optimize HU adherence, particularly in individuals with SCD facing challenges such as chronic pain. This study contributes significantly to understanding the factors influencing HU adherence and its broader implications for health-care utilization in the pediatric SCD population.[33]

The quasi-experimental study conducted by Ofakunrin *et al*. in Nigeria, involving 54 pediatric participants aged 4–17 years, sheds light on the effectiveness and safety of HU in managing SCD. The study's comprehensive findings indicate a noteworthy reduction in various complications associated with SCD, including vaso-occlusive crises, ACS, blood transfusions, and hospitalizations, coupled with a decrease in the duration of hospital stays. A particularly significant outcome is the substantial 46.3% decrease in painful crises, underscoring HU's potential to enhance the overall well-being of pediatric SCD patients. The observed reduction in leukocyte and platelet counts further supports the multifaceted benefits of HU in mitigating inflammatory processes. Notably, the study reports only two instances of leukopenia at a specific dose, affirming the overall safety and effectiveness of HU in the studied population. This research significantly contributes to the growing body of evidence supporting HU as a valuable therapeutic option in the comprehensive management of pediatric SCD, emphasizing its potential to reduce complications and improve overall patient outcomes.[34]

The double-blind randomized controlled trial conducted by Jain *et al*. in India, involving 60 participants aged 5–18 years, presents significant insights into the efficacy and safety of HU in the management of SCD. The study's outcomes reveal a positive impact on key hematological parameters, as reflected in increased HgbF levels and overall Hgb. Notably, the observed decrease in painful crises, blood transfusions, and hospitalizations underscores the therapeutic potential of HU in reducing the frequency and severity of complications associated with SCD. However, the study does report several adverse events, suggesting the need for careful consideration of potential risks in the administration of HU. Overall, these findings contribute valuable evidence supporting the effectiveness of a modest, fixed dose of HU in the treatment of individuals with SCD, emphasizing its potential to improve hematological parameters and mitigate the impact of clinical manifestations associated with the disease. Further research and monitoring are essential to refine dosage strategies and optimize the use of HU in diverse pediatric populations with SCD.[35]

The observational study conducted by Patel *et al*. in India, involving 27 participants aged 3–14 years, contributes significant insights into the utility of HU in the management of SCD. The findings of the study reveal a substantial 71.5% reduction in painful crises, a critical aspect of SCD symptomatology, further emphasizing the therapeutic potential of HU in ameliorating the clinical burden of the disease. Furthermore, the baseline values of Hgb, MCV, mean corpuscular hemoglobin concentration, and HgbF have all increased, which highlights the beneficial effects of HU on these important hematological parameters. Remarkably, these improvements were evident even at a minimal dose of 10 mg/kg/day, affirming the efficacy of HU in inducing favorable changes in both clinical and hematological domains at lower doses. This research contributes valuable evidence supporting the use of HU in the management of SCD, emphasizing its potential to reduce painful crises and enhance key hematological indicators, particularly at lower and potentially more tolerable doses. Further research and exploration are warranted to optimize dosing strategies and better understand the nuanced effects of HU in diverse SCD patient populations.[36]

The randomized multicenter trials conducted by Meier *et al*. in the USA, involving 116 participants aged 0.5–21 years, provide substantial insights into the disease-modifying effects of HU in SCA. The study's findings underscore the pivotal role of HU in altering the course of SCA, emphasizing its potential to reduce complications associated with the disease. Notably, the research emphasizes the significance of both the HU dosage strategy and the age at which the treatment is initiated. This implies that tailoring the dosage based on individual patient needs, coupled with initiating HU therapy at an appropriate age, holds paramount importance in achieving optimal outcomes. These observations reinforce the notion that HU serves not only as a symptomatic treatment but also as a disease-modifying agent in the context of SCA. This research contributes valuable insights into the potential benefits of HU as a disease-modifying treatment, shedding light on the importance of personalized dosing strategies and timely initiation for optimal outcomes in individuals with SCA. Further studies and long-term follow-ups are warranted to refine dosage recommendations and elucidate the sustained effects of HU in diverse age groups and SCA populations.[37]

The retrospective study conducted by Lobo *et al*. and published in the British Journal of Haematology, involving 267 participants aged 3–18 years in the USA, provides valuable insights into the impact of HU therapy on children with SCD. The study revealed a significantly higher survival rate among HU-treated patients in comparison to untreated counterparts, with fewer deaths attributed to ACS and infections. Despite observing a decrease in several hematological parameters, including Hgb concentration, HgbF, MCV, platelet count, and neutrophils, HU was associated with a reduction in the severity of the disease and a decrease in morbidity. These findings emphasize the positive impact of HU therapy in improving the overall well-being and survival of children with SCD. The study provides crucial evidence supporting the role of HU in mitigating the severity of SCD-related complications and underscores its potential to enhance the clinical outcomes and quality of life for affected children. Further research is warranted to explore the long-term effects and optimize the use of HU in diverse pediatric populations with SCD.[38]

The cohort study conducted by Keikhaei *et al*. and published in the Global Journal of Health Science, involving 48 participants aged 6–18 years in Iran, provides important insights into the effects of HU in individuals with SCD. The study revealed positive outcomes, with a notable decrease in the rate of hospitalization, transfusion requirements, and spleen size among the participants. In addition, there was a significant increase in Hgb, RBC count, and HgbF levels, indicating favorable hematological responses to HU treatment. Importantly, the study observed a substantial rise in HgbF, total Hgb, and RBC indices without any reported side effects, underscoring the safety and efficacy of HU in this cohort. These findings contribute valuable evidence supporting the benefits of HU in improving various clinical parameters and overall outcomes in individuals with SCD. The study highlights the potential of HU to reduce complications and enhance hematological profiles, emphasizing its role as a therapeutic option in the management of SCD. Further research and long-term monitoring are crucial to refine dosage strategies and optimize the use of HU in diverse populations with SCD.[39]

The single-center clinical trial conducted by Deshpande *et al*. and published in the Indian Journal of Haematology and Blood Transfusion, involving 10 participants aged 0–10 years in India, offers valuable insights into the efficacy of HU in the management of SCD. The study demonstrated positive outcomes, including a significant increase in HgbF, coupled with lower neutrophil and reticulocyte counts. Furthermore, HU treatment led to decreased adhesiveness and hemolysis, indicating a favorable impact on hematological parameters. Importantly, the trial concluded that HU is effective in reducing sickle cell crises and transfusion requirements, contributing to an enhanced overall quality of life for patients with SCD. These results highlight the significance of HU in improving hematological parameters and reducing clinical consequences, contributing to the increasing body of evidence that supports its efficacy in managing SCD. The study underscores the potential of HU as a therapeutic intervention, enhancing the well-being of individuals affected by SCD and highlighting the need for further research to refine treatment strategies and optimize outcomes.[40]

The retrospective study conducted by Reeves *et al*. and published in Clinical Pediatrics, involving a substantial cohort of 4435 participants aged 1–17 years in the USA, provides valuable insights into the impact of HU on medical visits and pain reduction in pediatric patients with SCD. The study revealed that HU usage was associated with a significantly decrease in various types of medical visits across different age groups, suggesting a potential positive effect on overall health-care utilization. Furthermore, the research highlighted a correlation between earlier initiation of HU and a reduction in pain experienced over the lifespan of a child with SCD. Despite these positive findings, the study identified a low prevalence of HU use among children, underscoring the existing challenges in promoting its adoption. This emphasizes the pressing need for targeted interventions to increase both the utilization and adherence to HU therapy in pediatric patients with SCD. Overall, the study contributes to the understanding of the potential benefits of HU in alleviating pain and improving health-care outcomes in this vulnerable population, emphasizing the importance of addressing barriers to its widespread implementation.[41]

The prospective study conducted by Di Maggio *et al*. and published in the International Journal of Molecular Sciences, focusing on a cohort of 30 participants aged 2–12.5 years in Yemen, provides substantial evidence supporting the effectiveness of HU in managing SCA in this specific population. The study demonstrated that the administration of low-dose HU (15 mg/kg/day) resulted in a significant decrease in vaso-occlusive crises, blood transfusions, hospitalizations, ACS, and cerebrovascular strokes. Notably, the intervention also led to an increase in Hgb levels and HgbF percentage, indicating positive effects on both clinical outcomes and hematological parameters. The findings of this research contribute to the broader understanding of HU's effectiveness in diverse populations and highlight its potential as a beneficial therapeutic option for managing SCA in Yemeni children. This underscores the importance of tailoring treatment strategies to specific demographic groups and reinforces the positive impact of HU in improving both clinical and hematological aspects of SCA management.[42]

Implication of study

The comprehensive review, "Comprehensive Insights into HU Treatment for Children with SCD: A Critical Review," holds several implications for clinical practice, research, and public health. First, the review synthesizes a diverse range of studies from various geographical locations, reflecting

a global perspective on HU treatment in pediatric patients with SCD. This inclusivity suggests that the findings and conclusions drawn from the review can be broadly applicable across different cultural and health-care contexts. From a clinical standpoint, the collective evidence presented in the review emphasizes the consistent positive outcomes associated with HU treatment in pediatric SCD patients. The reduction in ACS, vaso-occlusive crises, blood transfusions, and hospitalization duration, coupled with improvements in hematological parameters, underscores the drug's potential as a valuable therapeutic option. This insight is crucial for health-care practitioners, guiding them toward considering HU as an integral component in the comprehensive management of pediatric SCD. Moreover, the review highlights the diverse methodologies employed in the included studies, ranging from retrospective reviews to randomized controlled trials. This diversity suggests the need for a multifaceted approach in future research endeavors, catering to specific objectives and contexts. This implication encourages researchers to adopt rigorous and context-specific methodologies in their investigations, ensuring a holistic understanding of HU's safety and efficacy in diverse populations. In terms of public health, the review underscores the importance of expanding access to HU treatment, especially in low-income settings. The evidence supporting the drug's safety and efficacy in diverse populations, including those in Africa, Nigeria, India, and Yemen, calls for concerted efforts to make HU more widely available. This supports the inclusion of HU in national guidelines for the therapy of pediatric SCD, which has consequences for health-care policy and resource allocation. In summary, the critical evaluation offers a thorough synthesis of the body of knowledge about the use of HU in the treatment of SCD in children. Its consequences go beyond directing clinical judgments to affecting public health policies, future research endeavors, and clinical decisions to enhance the general health of juvenile SCD patients globally.

Future direction of study

The critical review, "Comprehensive Insights into HU Treatment for Children with SCD: A Critical Review," opens avenues for several promising future directions in research and clinical practice. Despite the wealth of information gathered in the critical review on HU treatment for children with SCD, certain research gaps persist, suggesting fruitful avenues for future investigation and advancement in this critical field.

Long-term safety and efficacy

The existing literature predominantly focuses on short-to-medium-term outcomes. Future studies should prioritize long-term follow-ups to comprehensively understand the enduring safety and efficacy of HU treatment in pediatric patients. This includes investigating potential late-onset adverse effects and evaluating its sustained impact on disease progression.

Optimal dosage and duration guidelines

The diverse dosage regimens and treatment durations reported in the reviewed studies underscore the need for standardized guidelines. Future research should aim to establish optimal dosage and duration parameters, considering factors such as age, disease severity, and geographical variations, to enhance treatment effectiveness and consistency.

Personalized treatment approaches

The heterogeneity within the pediatric SCD population suggests the necessity for personalized treatment strategies. Further investigations should explore how genetic factors, specific disease phenotypes, and individual patient characteristics influence the response to HU, enabling tailored therapeutic approaches for different patient profiles.

Comparative effectiveness studies

The review highlights a lack of head-to-head comparative studies evaluating HU against alternative treatments or in combination with other therapeutic modalities. Future research should prioritize well-designed comparative effectiveness studies to elucidate the relative benefits of HU and guide evidence-based treatment decisions.

Patient adherence and health-related quality of life

The impact of HU on patient adherence and health-related quality of life remains an understudied area. Future investigations should explore the psychosocial factors influencing adherence, develop interventions to enhance patient compliance, and assess the broader implications of treatment on the overall well-being and daily functioning of pediatric patients.

Global perspectives and resource-limited settings

The majority of studies are from high-resource settings, leaving a gap in understanding the challenges and opportunities associated with HU treatment in resource-limited environments. Future research must actively address the applicability, feasibility, and barriers to implementation in diverse health-care settings globally.

Impact on health-care utilization

The review hints at potential effects on health-care utilization, but this aspect requires more in-depth exploration. Future scientific studies must investigate the impact of HU treatment on emergency room visits, hospitalizations, and health-care costs, providing crucial insights for health-care policymakers and resource allocation.

By addressing these research gaps, future studies can refine our understanding of HU treatment in pediatric SCD, ultimately guiding clinical practice, informing policy decisions, and

improving outcomes for this vulnerable patient population. Exploring these future directions can contribute to refining treatment approaches, enhancing patient outcomes, and advancing the field toward more personalized and effective management strategies.

Strengths of the study

The review, "Comprehensive Insights into HU Treatment for Children with SCD: A Critical Review," exhibits several strengths. First, it provides a comprehensive analysis by synthesizing data from a diverse set of studies (108 references and 14 distinct articles), offering a global perspective on HU treatment. The inclusion of various research methodologies, spanning clinical trials to retrospective studies, enhances the robustness of the findings. The review encompasses a wide age range, reflecting the heterogeneity in pediatric SCD patients. In addition, by delving into safety, efficacy, and demographic aspects, the review offers a holistic understanding of HU's impact.

Limitations of study

Despite its strengths, the review has certain limitations. Variability in study designs, including differences in dosage regimens and treatment durations, may pose challenges in directly comparing outcomes. The reliance on existing literature introduces the possibility of publication bias, as negative or neutral results may not be as prominently represented. In addition, the review primarily focuses on short-term outcomes, necessitating caution in extrapolating findings to long-term effects. The heterogeneity in patient populations across studies, including differences in genetic backgrounds and environmental factors, could impact the generalizability of the conclusions. Lastly, while the safety profile is discussed, the review may benefit from more extensive exploration of potential long-term adverse effects and factors influencing adherence to HU therapy.

CONCLUSION

In conclusion, this critical review, "Comprehensive Insights into HU Treatment for Children with Sickle Cell Disease," illuminates the multifaceted landscape of HU therapy across diverse studies. Synthesizing data from 108 references and 14 distinct articles, the review offers a global perspective, encompassing varied geographical locations and demographic profiles. The findings underscore the consistent positive impact of HU in pediatric SCD, emphasizing reductions in vaso-occlusive crises, hospitalizations, and transfusions, along with improvements in hematological parameters. The inclusion of different study designs and patient cohorts enriches the depth of understanding. Despite inherent limitations such as potential publication bias and variations in study methodologies, this review serves as a valuable resource for clinicians, researchers, and policymakers. Moving forward, addressing the identified limitations, fostering long-term investigations, and exploring nuanced aspects of HU therapy will be crucial for refining its role in the comprehensive management of pediatric patients with SCD.

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ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not Applicable.

PATIENT CONSENT

Not Applicable.

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