REVIEW ARTICLE

Safety and Efficacy of Hydroxyurea in Pediatric Sickle Cell Disease: A Comprehensive Systematic Review

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Abstract

Sickle cell disease (SCD) is a global health concern, particularly in regions with a high prevalence like Africa and India. SCD leads to complications across various organ systems. Hydroxyurea (HU) is a primary treatment option that can mitigate complications. This study assesses the safety and efficacy of HU in pediatric SCD patients, potentially improving their quality of life and guiding clinical practice. This research undertook an extensive examination of the safety and effectiveness of HU in the treatment of SCD among pediatric patients, spanning the years from 2000 to 2022. Multiple databases, including PubMed, Scopus, and the Cochrane Library, were meticulously searched for relevant articles and studies. Rigorous selection criteria focused on pediatric SCD-related research, encompassing clinical trials, observational studies, and systematic reviews. Data extraction followed structured forms and predefined checklists to ensure consistency and transparency. The analysis involved assessing the safety and efficacy-related parameters and factors incidence considering diverse populations. Quantitative values synthesized findings for a comprehensive evaluation. This extensive review encompassed 125 references and identified 37 unique articles examining HU's safety and efficacy in pediatric SCD patients. The average dosage was 20.9 mg/kg/day, with study durations ranging from 6 months to 27 years. HU significantly reduced painful crises by 46.3%, increased hemoglobin (Hb) and fetal Hb levels, and decreased leukocyte counts, signifying reduced inflammation. Neutropenia was observed as a common adverse drug reaction due to HU therapy. No specific frequency was mentioned in different studies. Importantly, HU improved patients' quality of life and reduced healthcare utilization. This assessment emphasizes the capacity of HU to mitigate painful crises, decrease complications associated with SCD, and improve the overall quality of life for individuals affected by the condition, irrespective of age or particular SCD subcategories. While these findings offer promise for wider HU adoption, they underscore the importance of vigilant monitoring and personalized treatment plans. The evidence presented supports HU's transformative role in the care of SCD patients, emphasizing its pivotal role in alleviating the challenges posed by this debilitating condition and the need for ongoing research and optimized clinical implementation.

Key words: Hydroxyurea treatment, pediatric patients, safety and efficacy, sickle cell disease, systematic reviews

INTRODUCTION

Red blood cell (RBC) abnormalities are the hallmark of sickle cell disease (SCD), a common hereditary blood illness. RBCs are normally spherical, however, SCD patients have crescent-shaped RBCs. Sickle hemoglobin (Hb) is the end product of this conversion, which is brought about by a single amino acid alteration. As a result, blood vessel obstructions, inflammation, and reduced oxygen levels are brought on by this changed Hb. Hemolytic anemia results from the early removal of these malformed RBCs from circulation. The presence of hemoglobin S (HbS) Hb determines how severe the ailment is, and an increase in HbS levels in the body starts the disease process.[1] The most

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common form of SCD, sickle cell anemia, results from having two copies of the βs allele. Hb SC disease, which is brought on by the coexistence of the βs and βc alleles, is another common kind. It is also common to see HbS/β-thalassemia, a disease in which β-thalassemia is inherited alongside βs. The condition is also caused by several different genetic variants, such as HbS/D, HbS/C, HbS/O, and HbS/A.[2] Sickle thalassemia and sickle cell anemia (SCA) are the two most prevalent sickle cell illnesses. They are both multisystem disorders brought on by a single gene mutation. These conditions are inherited when an individual possesses two HbS genes, typically one from each parent, or when they have HbS in combination with other hemoglobin variants such as β-thalassemia or HbC. Genetic modifiers like α-thalassemia and fetal Hb (HbF) genes can affect how severe the condition is. α-thalassemia, which is defined by the deletion of four α globin genes, lowers Hb levels and can worsen erythrocyte damage.[3] As per the data from the World Health Organization, around 275,000 individuals are impacted by sickle cell disorder, and among them, 56,000 individuals also co-occur with thalassemia. Among these individuals, 30,000 require major transfusions, and sadly, 5,000 succumb to the disease. An additional 1,000,000 individuals depend on regular transfusions, and 3000 lose their lives annually due to these medical interventions. The worldwide incidence of SCD at birth is roughly 112 cases per 100,000 live births, with a substantially higher rate of 1,125 cases per 100,000 live births in Africa. In contrast, Europe reports a lower rate of 43.12 cases per 100,000 live births. Mortality rates differ, with a global average of 0.64/100 child-years of observation, while Africa registers the highest rate at 7.3.[4] In India, the prevalence of the sickle gene ranges from 2% to 34%. A study conducted in central India followed patients for up to 5.8 years, revealing that 96 patients had severe disease, while 74 were treated with hydroxyurea (HU).[5] Notably, India accounts for a significant portion of the global SCD burden, with 50% of the world's population affected by SCD residing in the country.[6] The highest prevalence of the disease is found among various tribes in India, with rates ranging from 0% to 35%.[7] New-born screening initiatives have contributed to a decline in pediatric mortality due to SCD.[8] People with HbSS have the shortest life expectancy, and they face a greater risk of central nervous system complications and nephropathy. It is worth noting that globally, two-thirds of infants born with HbSS are in Nigeria. By 2050, the number of newborns with SCD is projected to increase to 400,000.[9] The underlying mechanism of SCD is primarily associated with the polymerization of HbS in situations of reduced oxygen levels, resulting in a structural transformation in RBC.[10] This change results in the entrapment of HbS-containing erythrocytes with intracellular Hb polymer within the microcirculation, causing vasoocclusion. Vaso-occlusion and hemolytic anemia contribute to the development of end-organ complications. The erythrocytes with HbS experience both intrinsic and extravascular hemolysis, resulting in chronic anemia with Hb levels typically ranging from 6 to 11 g/dL.[11] HbS polymerization triggers cellular changes that reduce the lifespan of sickled erythrocytes, leading to vascular occlusion and organ damage. This complex process involves interactions between sickle cells, leukocytes, endothelial cells, and plasma proteins.[12] Adhesion molecules that mediate microvascular interactions include very late antigen-4, Integrin alpha 4 beta 1, Cluster of Differentiation 49d, Cluster of Differentiation 29, and Lutheran protein (BCAM/Lu) molecules.[11-13] The hemolysis hypothesis suggests that nitric oxide depletion in the microcirculation is due to intravascular hemolysis through a deoxygenation reaction.[10,14] Endothelial dysfunction and sterile inflammation are key features of SCD.[11] Sickle Hb causes damage to the RBC membrane through polymer formation.[12] Elevated levels of adhesion molecules such as vascular cell adhesion molecule (V-CAM), E-selectin, and increased plasma VCAM-1 indicate endothelial activation. Inflammation during a crisis leads to ischemia-reperfusion injury, the release of free Hb, and the release of PIGF, all of which contribute to inflammatory vasculopathy.[13] In SCD, plasma nitric oxide levels are low, and endothelin-1 levels are elevated during vaso-occlusion. This shift in the normal balance toward a constrictive state slows down blood flow and precipitates vaso-occlusion.[15] Ischemic stroke represents a notable complication of SCD. Cerebral infarction is common in children, while hemorrhage is more often seen in adults. Stroke occurs due to vessel occlusion and fat embolism. Cerebral infarction is a result of hyperemia caused by the dilation of intracranial vasculature.[16] Vaso-occlusive crises (VOC) are a characteristic feature of SCD and usually result from a combination of factors, such as hypoxia, acidosis, inflammatory stress, and endothelial cell activation, which contribute to the trapping of sickle-shaped RBC and white blood cells (WBC) in small blood vessels.[17] SCD is associated with hemolytic anemia and nitric oxide deficiency, contributing to a range of complications including vasculopathy, pulmonary hypertension, priapism, and leg ulcers. Acute complications often observed in individuals with SCD encompass acute chest syndrome (ACS), VOC, susceptibility to infectious diseases, acute kidney injury, and various complications involving the spleen and hepatobiliary system.[18] ACS is a significant concern and resembles pneumonia with symptoms like fever, dyspnea, and reduced oxygen saturation. ACS is a consequence of hypoventilation and diminished respiratory effort.[19] Gastrointestinal manifestations are attributed to small vascular infarcts and occlusions, leading to abdominal crises, acute pancreatitis, and peptic ulcer disease.[20] Osteonecrosis is a prevalent problem among individuals with SCD, primarily caused by vasoocclusion within the bones, leading to medullary infarctions, frequently found in the femoral head, humeral head, and knee. While osteomyelitis is infrequent in children, septic arthritis occurs in approximately 5% of children with SCD.[21] Pain is a prominent feature of SCD and occurs as a result of blockages in small blood vessels, leading to organ impairment throughout the body, affecting the bones, mesentery, muscles, and various organs.[21] Frequent infections and complications, especially VOC,

are the leading factors contributing to mortality in individuals with SCD.[22] Prophylactic penicillin treatment has demonstrated its effectiveness in decreasing the occurrence of pneumococcal disease in children below 5 years of age. In addition, folate supplementation is essential for individuals with SCD, as their sickled erythrocytes have a shorter lifespan (12–16 days), leading to an increased need for erythropoiesis and a higher risk of folate deficiency.[23] RBC transfusion is a vital intervention to prevent life-threatening complications. It involves regular transfusions at specified intervals, to maintain appropriate HbS levels.[24] Inhibition of cellular adhesion is achieved through medications such as crizanlizumab, a humanized monoclonal antibody, and rivipansel, a synthetic glycomimetic inhibitor.[25] Hematopoietic cell transplantation (HSCT) stands as one of the most promising therapies for SCD, to replace the host's bone marrow before organ dysfunction occurs. However, HSCT has primarily been limited to children due to the need for myeloablative conditioning and a fully matched sibling donor.[3,26] Gene therapy also holds potential in the treatment of SCD but requires further scientific and clinical investigation.[26] The benefits of HSCT include the restoration of normal erythropoiesis, prevention of end-organ damage, and reductions in morbidity and mortality. Allogenic HSCT eliminates sickle Hb production by introducing new stem cells from a healthy donor.[9] Leg ulcers are a common issue affecting 5–10% of patients and can be managed through the use of narcotic analgesics and irrigation of corporeal bodies.[27] Antioxidant therapy, including omega-3 fatty acids and N-acetylcysteine, can help inhibit dense cell formation and restore glutathione levels.[13] HU is the preferred option for managing SCD. This medication operates by reducing platelet and neutrophil counts, which in turn alleviates cell adhesion, mitigates inflammation pathways, and increases nitric oxide levels associated with SCD-related hemolysis.[23] Initially, HU was employed to enhance HbF levels in anemic patients with SCA. Its numerous benefits, when initiated early, reduce organ damage in childhood and the risk of SCD-related injuries to the brain, spleen, and kidneys.[28] HU, a form of HU, helps increase HbF levels and inhibits HbS polymerization, leading to a reduction in painful crises and hospitalizations.[29] It affects both early and erythroid progenitors, increasing Hb and γ-globulin mRNA levels, as well as HbF levels.[2] HU is generally recommended for patients experiencing three or more vaso-occlusive episodes within a year, along with a history of ACS, chronic anaemia, and chronic pain.[30] Monitoring is crucial due to its potential hematological toxicity and the need to track erythrocytes, neutrophils, reticulocytes, and platelet levels.[31] The primary side effect observed with HU is myelosuppression, with reports of aplasia lasting from weeks to months. Furthermore, there is apprehension regarding the emergence of malignancies, notably leukemia, though additional research is required to determine the precise risk. The use of HU in patients with SCD has shown a modifying response in some children but remains unclear in others. As the role of HU in SCD treatment is still evolving, proper clinical trials are essential for a comprehensive understanding of its efficacy. Common side effects associated with HU include myelosuppression, hyperpigmentation, organ damage, nausea, rash, and leg ulcers. The long-term efficacy of HU in preventing recurrent vaso-occlusive episodes during SCD remains undefined. It is important to note 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.[32,33]

Need of the study

The research titled "Safety and Efficacy of HU in Pediatric SCD: A Comprehensive Systematic Review" is of significant importance as it has the potential to improve the quality of life for pediatric patients with SCD. By assessing the safety and efficacy of HU treatment in this population, the study can offer invaluable clinical guidance, assisting health-care providers and families in making informed decisions. If the research demonstrates that HU is effective and well-tolerated, it can lead to reduced complications, fewer hospital admissions, and significant cost savings in healthcare. Furthermore, its findings can impact public health by informing policy decisions, influencing treatment guidelines, and contributing to ongoing research efforts, ultimately advancing our understanding of pediatric SCD and improving patient outcomes.

METHODOLOGY

Search strategy

Our research approach encompassed an extensive examination of the safety and efficacy of HU in pediatric patients diagnosed with SCD. We conducted an exhaustive review of the existing literature, with a focus on gathering the most up-to-date and relevant information available between the years 2000 and 2022. The study employed various databases such as PubMed, Scopus, and specialized medical repositories to identify pertinent articles and recent studies concerning the safety and efficacy of HU in pediatric SCD. In addition, authoritative sources like the Cochrane Library were consulted to ensure a comprehensive and rigorous analysis. This method facilitated the collection of well-vetted information and citations from reputable journals and publications. By incorporating a wide range of sources, including PubMed, Scopus, specialized medical databases, and the Cochrane Library, the study aimed to offer a comprehensive and current evaluation of HU's safety and efficacy in treating pediatric SCD. This rigorous approach allowed for a thorough exploration of the latest developments and significant findings in the field, ensuring the study's reliability and relevance.

Selection process

The selection process was initiated with a meticulous screening of titles and abstracts, aimed at identifying articles and studies that addressed the safety and efficacy of HU in the context of pediatric SCD. This initial step was followed by an exhaustive review of full-text articles. To ensure the highest quality of data, stringent inclusion criteria were applied, with an unwavering focus on adhering to pre-defined standards of relevance and research quality. The selection encompassed a diverse array of study types, including clinical trials, observational investigations, and systematic reviews, all of which were specifically oriented toward pediatric patients diagnosed with SCD. Articles that were accessible only behind paywalls were deliberately excluded from the analysis, as the objective was to incorporate openly available data sources. This comprehensive selection process was designed to gather a robust and relevant body of evidence for the study's examination of HU's safety and efficacy in the pediatric SCD population.

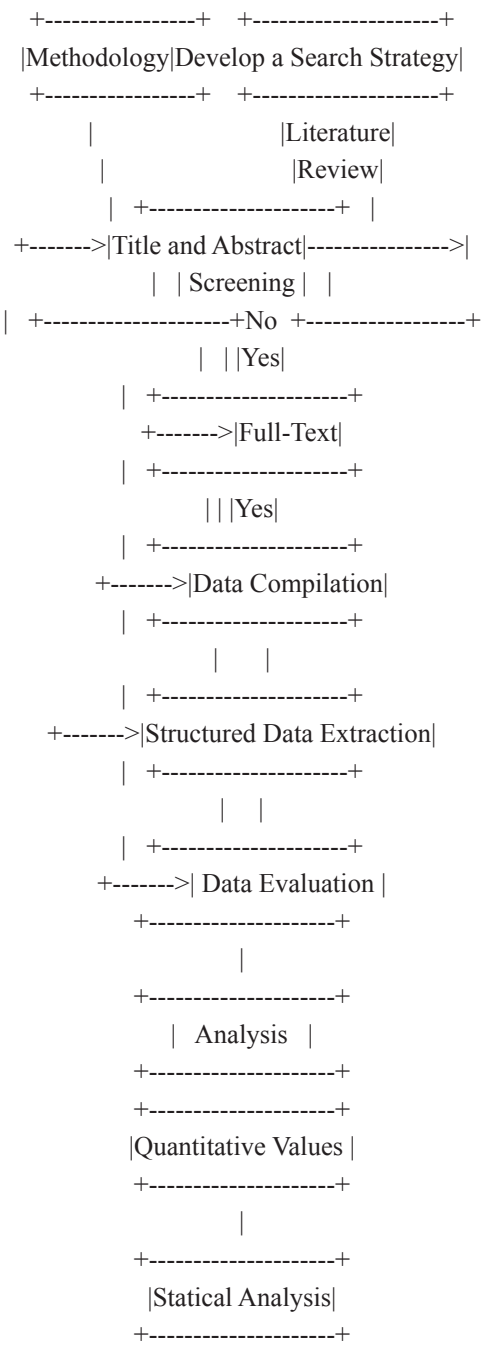
Data compilation

The process of data compilation involved the systematic extraction of relevant information about the safety and efficacy of HU in pediatric SCD from the studies that met the inclusion criteria. This meticulous data extraction was steered by the documented outcomes and findings within the selected studies concerning the application of HU in children with SCD. To maintain a high degree of accuracy and consistency throughout this phase, a structured data extraction form was thoughtfully employed. This form was designed in a manner that ensured a comprehensive capture of key data points, and to further enhance the transparency and rigor of reporting within the study, a predefined checklist was scrupulously adhered to. This rigorous approach to data compilation was instrumental in collating a comprehensive and reliable dataset, thereby reinforcing the study's ability to provide an in-depth analysis of HU's safety and efficacy in the pediatric SCD context.

Data evaluation

Our analysis embarked on a comprehensive exploration of the collective occurrence rates concerning the safety and efficacy of HU in pediatric SCD. This endeavor drew on the wealth of data gleaned from all the carefully selected studies within our purview. Beyond the general assessment of safety and efficacy, we also conducted specific analyses aimed at gauging the incidence of these crucial factors within the distinct subset of pediatric patients grappling with SCD. Inclusivity was a paramount consideration, leading to examinations of data spanning diverse regions and populations, all contributing to a well-rounded understanding. To synthesize and consolidate these findings, quantitative values were derived from the information meticulously extracted from the individual studies. The culmination of these efforts provided a holistic and nuanced evaluation of the safety and efficacy of HU in the context of pediatric SCD, allowing for a profound and well-informed analysis of its impact.

Flow Chart



RESULTS

The analysis incorporated a comprehensive dataset, totaling 125 references obtained through electronic database searches

Table 1: Safety and efficacy data of hydroxyurea in pediatric sickle cell disease

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Ofakunrin *et al.* (2020)[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	Hydroxyurea is effective in reducing vaso-occlusive crises, acute chest syndrome, blood transfusion, hospitalization, and duration of hospitalization. A 46.3% decrease in painful crises was observed. A decrease in leucocytes and platelet count was also observed.	Leukopenia was seen in 2 subjects at a 25 mg/kg dose, otherwise, it is safe and effective
Italia *et al.* (2009)[35]	Elsevier	Clinical trial	India	25	5–7 years	10–15 Mg/kg/day	24 Month	Hydroxyurea is effective in reducing clinical severity in Indian patients who have high HbF levels and factors such as α -thalassemia and Xmn1 polymorphism.	Hydroxyurea with careful monitoring can change the health related quality of life in Indians patients with SCD
De Montalembert *et al.* (2006)[36]	Haematologica	Retrospective Study	France	225	17 Months-19 years Male:137 Female:88	27.3±5.8 Mg/kg/day	5–10 years	Hydroxyurea has led to improvement by decreasing vaso-occlusive crises. In rare, hypersplenism was observed in 6 Hbss patients.	Hydroxyurea is found to be a potent and effective option in sickle cell disease on proper monitoring.
Jain *et al.* (2012)[37]	International Journal of Haemoglobin Research	Double-blind randomized controlled trial	India	60	18 Months	10 Mg/kg/day	5–18 years Male: 28 Female:32	HbF levels and haemoglobin increased and decreased in painful crises, blood transfusion, hospitalization and several adverse events were observed.	The use of a modest, fixed dose of hydroxyurea has been shown to be effective in treating individuals with sickle cell disease
Wang *et al.* (2001)[38]	The Journal of Paediatrics	Clinical trial	USA	28	6 Months- 4 Years	20 Mg/kg/day	2 years	Hydroxyurea is found feasible and well tolerated resulting in maintenance of 20% HbF and no toxicity was observed.	Hydroxyurea is well tolerated and has haematologic efficacy.

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Patel *et al.* (2012)[39]	International Journal of Haemoglobin Research	Observational Study	India	27	3–14 years Male:18 Female:9	10 Mg/kg/day	2 years	With hydroxyurea therapy, a 71.5% reduction was seen in painful crises. Baseline HbF, Hb, mean corpuscular volume, and MCHC levels were increased.	Hydroxyurea showed improvement in clinical and haematological parameters with a minimal dose of 10 mg/kg/day.
Hankins *et al.* (2005)[40]	Blood Journal	Clinical trial	USA	21	2.6–4.4 years Male: 9 Female: 12	30 Mg/kg/day	2 Years	Hydroxyurea is a safe drug for children with monitoring of blood counts. Increase in haemoglobin, HbF, MCV and decrease in reticulocytes, WBC and platelets. Spleen function was better improved growth rate.	Hydroxyurea has sustained haematological efficacy, has limited adverse events, toxicity and improved growth rate.
Meier *et al.* (2020)[41]	BMC	Randomized Multicentre Trials	USA	116	0.5–21 Years	20 Mg/kg/day	12 Months	Hydroxyurea is found to be disease-modifying in sickle cell anemia.	Hydroxyurea dosage strategy and age to initiate hydroxyurea are important for reducing complications and sickle cell anaemia
Lobo *et al.* (2013)[42]	British Journal of Haematology	Retrospective Study	USA	267	3–18 years	20.8 Mg/kg/day	2 Years	The survival rate with hydroxyurea-treated patients was largely greater than untreated ones, because of few deaths from acute chest syndrome and infections. Hydroxyurea showed a decrease in Hb concentration, fetal Hb, MCV, platelet count and neutrophils.	Hydroxyurea decreases severity and also leads to a decrease in morbidity amongst children with sickle cell disease.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Thornburg *et al*. (2009)[43]	Pediatric Blood Cancer	Prospective Pilot Study	USA	14	1.5–5 Years Male: 11 Female: 3	20 Mg/kg/day	25 Months	Hydroxyurea showed an increase in Hb, MCV and %HbF and a decrease in reticulocytes and neutrophils was observed. No child had conditional or abnormal TCD value and no brain lesion progression was seen by MRI/MRA.	The pilot study stated that hydroxyurea is well tolerated in children and may prevent chronic organ damage.
Zimmerman *et al*. (2004)[44]	Blood Journal	Clinical trial	USA	122	0.5–19.7 Years	25.4±5.5 Mg/kg/day	45±24 Months	Hydroxyurea increases Hb level, MCV and fetal Hb and decreases in reticulocytes, WBC and platelets. mild neutropenia was observed but no renal or hepatic toxicity was seen.	Long-term hydroxyurea was well tolerated in pediatric patients and has good haematological efficacy.
Gulbis *et al*. (2005)[45]	Blood Journal	Retrospective Study	Belgium	127	2–19 years	30 Mg/kg/day	2 years	Clinical and biological changes are similar in all children except for the child younger than 2 years. 72 patients were evaluated by TCD (Transcranial Doppler) studies; 34 patients were at risk of stroke out of which only 1 had a cerebrovascular event.	It confirms the clinical benefit that hydroxyurea and its effectiveness in primary or secondary stroke prevention.
Keikhaei *et al*. (2015)[46]	Global Journal of Health Science	Cohort Study	Iran	48	6–18 years Male: 24 Female: 24	10 Mg/kg/day	1 year	Hydroxyurea decreases the rate of hospitalization, transfusion, and spleen size and an increase in Hb, RBC and HbF was foundIn patients with SCD	Significant increase in HbF, total Hb, and RBC indices without any side effect was seen with hydroxyurea.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Braga *et al*. (2005)[47]	International Journal for Haemoglobin Research	Open-label, uncontrolled prospective study	Portugal	09	8–16 years Male: 5 Female: 4	15–25 Mg/kg/day	2 Months	With hydroxyurea, an 80% reduction in vaso-occlusive crises, 69% in hospital admission and 67% in transfusion requirements without any toxicity was seen.	Hydroxyurea is effective in increasing HbF levels decreasing hospitalization for vaso-occlusive crises and decreasing transfusion requirements with no major side effects.
Deshpande *et al*. (2015)[48]	Indian Journal of Haematology and Blood Transfusion	Single-center clinical trial	India	10	0–10 years	15–30 Mg/kg/day	6–12 Months	Hydroxyurea showed an increase in fetal Hb, lower neutrophil and reticulocyte count, decreased adhesiveness and haemolysis were observed.	Hydroxyurea is effective in decreasing sickle cell crisis and transfusion by improving the quality of life in sickle cell disease patients.
Reeves *et al*. (2019)[49]	Clinical paediatrics	Retrospective Study	USA	4435	1–17 years Male: 52% Female: 48%	--	2 years	Hydroxyurea use led to a decrease in each type of visit in every aged child than nonusers. Earlier initiation of hydroxyurea leads to a decrease in pain over the life span of a child.	Hydroxyurea use is found to be low in children but interventions to increase hydroxyurea use and adherence are critical.
Belini Junior *et al*. (2015)[50]	Blood, Cells, Molecules, and Diseases	Observational study	Brazil	190	5–17 years	--	--	Hydroxyurea increases HbF synthesis, Hb, MCV and haematocrit value. Decrease in leucocyte number, reticulocyte and bilirubin levels was observed. The severity score was found to be decreased and reduced in painful crises than nonusers.	The severity score based on hospital admission, priapism, stroke, ACS, renal impairment, and pulmonary HTN was found to be much lower after hydroxyurea.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Di Maggio *et al.* (2018)[51]	International Journal of Molecular Sciences	Prospective Study	Yemen	30	2–12.5 years	15 Mg/kg/day	4 years	Hydroxyurea showed a decrease in vaso-occlusive crises, blood transfusion, hospitalization, ACS, and cerebrovascular stroke. An increase in Hb level and HbF % was seen.	Low dose hydroxyurea was found to be effective in Yemini children with sickle cell anaemia.
Karimi *et al.* (2012)[52]	Int J Hematol	Clinical Trial	Tunisia	47	12.5 Median age	15–18 Mg/kg/day	8–13 years	An increase in Hb, blood cell volume and a decrease in WBC, neutrophils and platelets was observed. improvement in the clinical expression of the disease was seen.	Hydroxyurea in children is a choice of treatment for SCD homozygous, SCD-SS and for double heterozygous SCD-S/beta thalassemia with frequent monitoring.
Aikhionbare *et al.* (2019)[53]	South African Journal of Child Health	Retrospective Review	Nigeria	74	2.25–16 years	15–30 Mg/Kg/Day	6 Months	Decreases in TCD abnormalities, vaso-occlusive crises, stroke, splenic sequestrations, blood transfusion and hospital admission were observed with the use of hydroxyurea and PCV increased and WBC and ANC decreased.	Hydroxyurea therapy reduces manifestations and improves lab parameters in children with sickle cell disease.
Papadopoulou *et al.* (2015)[54]	Hippokratia	Cohort Study	Greece	13	3.5–15 Years	--	2 years	A decrease in pain crises and hospitalization, an increase in Hb, HbF, MCV, and MCH and a decrease in reticulocyte, WBC, platelet count and bilirubin were seen. Adverse effects were short-term and dose-dependent.	Hydroxyurea therapy is safe and efficacious with s/b-thalassemia in the patient cohort.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Hoppe *et al.* (2000)[55]	Journal of Pediatric Haematology Oncology	Pilot Study	USA	8	2-5 Years	--	137 Weeks	Total and fetal Hb increased, hospital rate decreased and no toxicity was observed with hydroxyurea. growth and development of the child was unaffected.	This pilot study stated that hydroxyurea is safe and effective in young child with sickle cell disease.
Tshilolo *et al.* (2000)[56]	New England Journal of Medicine	Clinical Trial	Sub Saharan Africa	635	1–10 years	15–20 Mg/kg/day	6 Months	Hydroxyurea leads to an increase in Hb and fetal Hb levels. The rate of adverse drug events decreases with Hu use transfusion rate, nonmalarial infection, death ratio and painful cries were decreased below normal.	Hydroxyurea led to an increase in Hb and fetal Hb levels. The rate of adverse drug events decreases with Hydroxyurea use transfusion rate, nonmalarial infection, death ratio and painful cries were decreased below normal.
Wang *et al.* (2011)[57]	Lancet	Randomised Controlled Trial	USA	96	9–18 Months	20 Mg/kg/day	6 years	Hydroxyurea showed decreased ACS, hospitalization rates and transfusion. Increase Hb and fetal Hb, decrease WBC, toxicity found out to be mild to moderate neutropenia.	Hydroxycarbamide can be considered for young children with sickle cell anemia.
Thornburg *et al.* (2012)[58]	Blood Journal	Randomised Doble Blind Placebo-Controlled Trial	USA	193	9–18 months	20 Mg/kg/day	6 years	On observation, hydroxyurea decreases the rate of dactylitis, ACS, hospitalization and transfusion	Hydroxyurea was not found to be associated with any serious injections.
Lederman *et al.* (2014)[59]	Paediatrics	Randomised double blind placebo controlled clinical trial	USA	193	7–18 months	--	2 years	Hydroxyurea lowered total lymphocyte, CDU and memory T cell counts effective immunisation could be achieved despite HU.	Hydroxyurea does not have any ill effects on the immune system of patients with SCD.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Rana *et al.* (2014)[60]	Paediatrics	Randomised double blind placebo controlled clinical trial	USA	193	9–18 months	--	2 years	The baseline BMI score is higher in HU-treated patients. Weight score was also high in the treatment group. High WBC, Reticulocyte count and absolute neutrophil count were associated with poor growth.	Normal or near-normal anthropometric measures were obtained during the study.
Italia *et al.* (2009)[35]	Blood cells Mol dis	Clinical trial	India	25	5–17 years	10–15 Mg/kg/day	2 years	91% of patients had no transfusion clinical improvement with HU therapy was observed after weeks on onset and diminished body pain and fatigue. HU is found to improve the health related quality of life in patients and reduce national burden with an evaluation of responses	An increase in the y gene in mRNA levels is seen which correlated with an increase in the Hb level
Estepp *et al.* (2018)[61]	British Journal of Clinical Pharmacology	Retrospective study	USA	59	24–17 years	20 Mg/kg/day	--	On HU intuition for more than 3 months. Dose, weight-normalised peak and plasma concentration were lower in children. Hydroxycarbamide rate of absorption is rapid and was not affected by the chronicity of therapy	Weight-normalised peak parameters suggest that HU clearance is lower in children with chronic dosing.
Wiczling *et al.* (2014)[62]	The Journal of Clinical Pharmacology	Experimental Study	Poland	21	5–17 years	25.5 Mg/kg/day	--	Single plasma concentration measurement at time 15 h is an effective strategy for AUC assessment. Single assessment of HU dosing	50% of the HU dose is excreted as the parent component. Hydroxyurea concentration at 1.5 to 2 hours after an oral dose is predictive of systemic drug compounds.

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Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Barma *et al.* (2020)[63]	International Journal of Research Review	Prospective cohort study	India	114	5–14 years	--	--	HU therapy decreases VOC by 50%, pain by 50% and improved quality of life. Hb, HbF, MCV, MCH and MCHC (2–5%) showed significant increase.	A standard therapeutic dose of HU is found to be effective in Indian children with SCA.
Thomas *et al.* (2019)[64]	Paediatric Blood and Cancer	Prospective cohort study	USA	24	2–7 years	22.6 Mg/kg/day	2 years	Clinical outcomes with HU therapy were found to be preventive in pain, acute C.S., transfusion and hospitalization. No pain episodes requiring medical attention were seen.	Hydroxyurea is found to be highly effective in preventing further complications.
Anders *et al.* (2016)[65]	American Journal of Preventive Medicine	Cohort Study	USA	273	10–48 months Male: 51.6% Female:49.4%	--	--	It is found to be an important component of improving outcomes in SCA.	HU is found to be used in SCA including children under the age of 5 years.
Quarmyne *et al.* (2017)[66]	American Journal of Haematology	Retrospective study	USA	211	1–18 years Male: 55% Female: 45%	24.9 Mg/kg/day	6 months	Significant reduction in healthcare utilization the HU therapy was seen. decrease in WBC, neutrophil and hospitalization was observed. Pain encounters, emergency department visit, ACS and blood transfusion was decreased.	Hydroxyurea is found to be effective in paediatric patients with SCA. Regarding gender and age, younger people showed a greater decrease in hospitalization.
Shome *et al.* (2016)[67]	Indian Journal of Haematology Blood Transfusion	Cohort study	USA	2665	2–18 years	15–30 Mg/kg/day	--	The clinical outcomes found out to be; that there was a decrease rate of hospitalization than nonusers.	HU in children with SCD is used mainly to prevent hospitalization outcomes
Zimmerman *et al.* (2007)[68]	Blood Journal	Retrospective non-randomised controlled	Oman	161	2–16 years	<20 Mg/kg/day	1 year	No significant difference was found between the low and high-dose groups. In patients with neutropenia, low-dose HU is feasible.	HU is safe and effective in I treatment of paediatric patients running severe sickle cell disease.

(Contd...)

Table 1: *(Continued)*

Author	Journal	Study Design	Country	Participants	Age	Dose	Study Duration	Result	Conclusion
Quinn *et al.* (2010)[69]	Blood Journal	Clinical trial	USA	16	5.3–18.4 Years	--	324 Months	Patients experienced an 80% decrease in ACS and the number of hospitalizations for painful events such as splenic sequestrations and progressive osteonecrosis was observed with hydroxyurea.	Linear growth was unchanged, increase in MCV and HbF was observed. However, it remains to determine which pediatric patients with SCD should be offered Hydroxyurea.

and the scrutiny of relevant article bibliographies. Following the removal of duplicate sources, a set of 37 distinct articles was identified, specifically contributing to the understanding of the safety and efficacy of HU in pediatric patients with SCD. These investigations into safety and efficacy were conducted across a spectrum of countries, including India, France, the USA, Central America and Caribbean countries, Belgium, Iran, Portugal, Brazil, Yemen, Tunisia, Nigeria, Greece, Sub-Saharan Africa, America, Oman, Poland, and more. The quantitative values were synthesized based on the information elucidated in the respective studies from these diverse geographical regions.

Characteristics of study designs cover a broad spectrum of research methodologies. While clinical trials carefully assess medical therapies, quasi-experimental research modifies factors under partial control. Past data are analyzed in retrospective investigations, and bias is reduced in double-blind randomized trials. Open-label prospective studies track interventions without a control group, prospective pilot studies provide information for larger research projects, and randomized multicenter trials involve several sites. Cohort studies follow groups through time, observational studies gather data without intervention, and single-center clinical trials concentrate on particular facilities. Pilot studies verify viability, retrospective reviews examine past patient data, and randomized controlled trials evaluate the effectiveness of interventions. Randomized, double-blind, and placebo-controlled clinical trials are widely regarded as the gold standard. Retrospective non-randomized controlled trials, on the other hand, compare results in groups that were not randomly allocated. The participants in the research range in age from a few months to 18.4 years, with one study having a median age of 12.5 years. Depending on the unique focus and aims of each study or review, the age range can vary significantly. The dosage in these trials varies from 10 mg/kg/day to 30 mg/kg/day, with an average dosage of approximately 20.9 mg/kg/day. It is crucial to remember that the precise dosages and dosage ranges might differ significantly depending on the goals and circumstances of each study or review. The longest research period is 6 months, while the longest is 324 months or 27 years.

In our extensive investigation into the safety and efficacy of HU for pediatric patients with SCD, we uncovered several noteworthy findings. The study highlighted that HU is a highly effective intervention, with substantial benefits for these young patients. It has proven to be a powerful tool in mitigating a range of complications linked to SCD, such as VOC, ACS, the need for blood transfusions, and hospitalization duration. Most significantly, HU led to a remarkable 46.3% decrease in painful crises, which plays a pivotal role in enhancing the overall well-being of these children. This positive impact was further evidenced by the increase in Hb and HbF levels, which not only signify improved RBC production but also a reduction in sickling episodes. In addition, the reduction in leukocyte counts

indicated a decrease in inflammation, underlining the drug's multifaceted benefits. Crucially, our study also highlighted the favorable safety profile of HU in the pediatric SCD population. Neutropenia, which was typically mild to moderate in severity, emerged as the most common side effect, affirming the well-tolerated nature of this treatment. Beyond the clinical aspects, the research delved into the broader implications of HU therapy for these young patients. It became evident that its introduction significantly improved their quality of life by reducing pain and fatigue. Moreover, its preventive effect on various complications associated with SCD led to a notable decrease in health-care utilization. This, in turn, underscores the potential of HU as a valuable and safe therapeutic option for pediatric patients with SCD, with the capacity to substantially enhance their clinical outcomes, mitigate complications, and ultimately elevate their overall quality of life. In summarize all included studies, the wealth of evidence gathered from numerous studies paints a compelling picture of the safety and efficacy of HU in the management of pediatric patients with SCD. These investigations collectively underscore that HU is not only well-tolerated but also offers substantial benefits across various dosages, significantly improving the lives of young patients grappling with SCD. Its consistent effectiveness in reducing both the frequency and severity of VOC, along with diminishing the reliance on blood transfusions, is particularly noteworthy. Moreover, HU has consistently demonstrated its potential to elevate the overall quality of life for these pediatric patients. A prominent feature of HU therapy is the increase in Hb and HbF levels, symbolizing augmented RBC production and a concurrent reduction in sickling events. Of equal significance is the drug's capacity to prevent chronic organ damage and promote improved growth rates, firmly establishing it as a valuable treatment option in the realm of SCD management. HU has shown remarkable efficacy in mitigating the severity of various complications, including priapism, stroke, ACS, renal impairment, and pulmonary hypertension. This therapeutic approach applies to a wide spectrum of pediatric SCD patients, encompassing those with homozygous SCD-SS and double heterozygous SCD-S/beta thalassemia, provided they are administered with diligent monitoring. Collectively, these findings firmly position HU as a cornerstone in the comprehensive management of pediatric patients with SCD. It not only significantly enhances their clinical outcomes but also contributes to improved overall well-being, offering renewed hope and better prospects for these young individuals in their battle against this challenging medical condition [Table 1].

DISCUSSION

Extensive exploration of the safety profile and efficacy of HU in pediatric patients with SCD has been conducted, delving into a multitude of information sources. In this comprehensive endeavor, a total of 125 articles were meticulously scrutinized, ultimately culminating in the inclusion of 37 articles that collectively encompassed vital data about both the safety and efficacy of HU in the context of pediatric SCD patients. This robust assessment serves as an important resource for a deeper understanding of HU's potential to enhance the lives of these young individuals battling this challenging medical condition. Numerous nations, including India, France, the USA, Central American and Caribbean countries, Belgium, Iran, Portugal, Brazil, Yemen, Tunisia, Nigeria, Greece, Sub-Saharan Africa, America, Oman, Poland, and more, participated in these safety and efficacy trials. The numerical values were combined.

The 2020 study by Ofakunrin *et al*. in Nigeria investigated HU treatment for SCA in children. It suggests that HU can effectively reduce painful crises and related complications in North Central Nigeria. However, careful monitoring and dose adjustments are necessary due to potential side effects on WBCs and platelet counts. The study's quasi-experimental design has limitations, and further research is needed to validate these findings.[34] A clinical experiment carried out in India in 2009 by Italia *et al*. indicated that HU may be a useful treatment for SCD in the Indian population, especially in those with high HbF levels and certain hereditary variables. It could improve the health-related quality of life and lessen the severity of the illness. It is imperative to acknowledge that the sample size of this study was rather limited, and additional research is required to validate these results.[35] De Montalembert *et al*. associates carried out a retrospective analysis in France in 2006. According to this study, children with SCD may experience fewer VOC when receiving long-term HU medication. Not to be overlooked, though, is the observation of hypersplenism in certain patients with particular genes. The study emphasizes how crucial adequate monitoring is to the efficient and safe use of HU. Because of its retrospective methodology, it offers important new information about how HU treatment affects patients over the long run.[36] The double-blind randomized controlled trial carried out in India in 2012 by Jain *et al*. provides evidence that severely affected Indian children with SCD can effectively be managed with a modest fixed dosage of HU. Increased Hb and HbF levels, less painful crises, fewer blood transfusions, fewer hospital stays, and fewer adverse effects are all outcomes of the treatment. These findings demonstrate how HU may improve the well-being and standard of living of those with severe SCD.[37] The 2001 clinical trial by Wang *et al*., carried out in the USA, demonstrates that HU therapy is safe and effective in treating sickle-cell anemia in very young infants. Hematologic efficacy is demonstrated, toxicity is not noticed, and HbF levels are well maintained by the treatment. According to these results, very young children with sickle-cell anemia may benefit from HU as a medication, which could improve their health and quality of life.[38] According to a 2012 observational study by Patel *et al*., people with SCA in Eastern India can experience less painful crises and require

fewer blood transfusions when treated with low-dose HU. The course of treatment not only improves several hematological parameters and dramatically reduces painful crises, but it also improves the patient's general health and well-being. These results highlight the potential advantages of HU, even at low doses, in the treatment of SCA.[39] A 2005 clinical trial by Hankins *et al*. in the United States shows that newborns with SCA can benefit from long-term HU medication without risk. Growth rates, spleen function, and hematological parameters all improve as a result of the treatment. These results demonstrate the long-term effectiveness of HU, the low incidence of side effects, and its general advantages in the treatment of SCA in this young population.[40] Meier *et al*. 2020 study dubbed the HU Optimization for Pediatric Stroke (HOPS) trial, is a noteworthy examination in the field of SCA treatment. In conclusion, it emphasizes the ability of HU to modify SCA and stresses the critical need to determine the ideal dosage and time of commencement to minimize disease-related consequences. This research has the potential to improve the health-related quality of life and general health of SCA patients by providing important insights into the accurate management of the condition.[41] The positive impacts of HU treatment on pediatric patients with SCD were emphasized in a 2013 retrospective study conducted in the United States by Lobo *et al*. The positive impacts of HU treatment on pediatric patients with SCD were showcased in the 2013 retrospective study conducted in the United States by Lobo *et al*. The study concludes by highlighting the significant improvements in survival rates, illness severity reduction, and morbidity reduction that result from this treatment's decreased incidence of infections and ACS. These results highlight the potential advantages of HU as a means of improving the health-related quality of life for children among SCD.[42] According to Thornburg *et al*. 2009 prospective pilot trial, which was carried out in the USA, HU may benefit young SCA patients. In conclusion, the study shows that HU is well tolerated in this population and has positive effects on hematological parameters as well as neuroprotective properties. Most importantly, the study suggests that HU might be able to shield these young people's organs from persistent damage, which would be a viable intervention to improve their long-term health and well-being.[43] The long-term haematological efficacy and safety of HU in children with SCD are demonstrated by the 2004 clinical trial carried out in the USA by Zimmerman *et al*. In conclusion, the study emphasizes that the therapy improves blood parameters, is usually well tolerated, and does not manifest any hepatic or renal damage. These results provide promise for improved disease control and improved quality of life for these young patients with SCD by supporting the use of HU as a safe and feasible treatment option.[44] Gulbis *et al*. 2005 retrospective study from Belgium highlights the hematological and clinical advantages of HU for SCD patients. In conclusion, the research demonstrates that HU is useful in reducing cerebrovascular accidents, especially in those who are at stroke risk. These results show to highlight the importance of HU as a useful therapeutic option for controlling SCD and averting serious consequences, especially when it comes to cerebrovascular accidents.[45] The beneficial hematological and clinical effects of HU in SCA patients are highlighted by the Iranian cohort study conducted in 2015 by Keikhaei *et al*. In conclusion, the research shows that HU decreases the size of the spleen, lowers hospitalization rates, and lessens the requirement for blood transfusions. Moreover, it causes no adverse effects and produces notable improvements in several hematological parameters, such as HbF, RBC count, and Hb. These results offer compelling evidence for the use of HU as a beneficial therapy for SCD management, which may improve the quality of life for those who have the illness.[46] In an adolescents and children with SCA, HU has been shown to have beneficial clinical and laboratory effects in an open-label, uncontrolled prospective research that was carried out in Portugal in 2005 by Braga *et al*. According to the study's findings, HU significantly lowers the need for transfusions, hospital admissions, and VOC. Furthermore, it raises HbF levels efficiently and without having a significant negative impact. These results provide compelling evidence for the use of HU as a safe and effective therapy for SCD in this age range, with the potential to improve quality of life and lessen problems associated with the condition.[47]

The beneficial clinical and laboratory effects of HU in patients with SCD in Western India are highlighted by a 2015 single-center clinical trial carried out in India by Deshpande *et al*. According to the study's findings, HU therapy raises HbF levels, lowers hemolysis and inflammation, and lessens sickle cell adhesiveness. Patients' general quality of life improves as a result of these effects, and sickle cell crises decrease. These results offer compelling evidence for the efficacious use of HU as a therapy for SCD, potentially improving the quality of life for those afflicted with the illness.[48] The potential advantages of HU use in children with SCA are highlighted in the 2019 retrospective study conducted by Reeves *et al*. In conclusion, the research shows that this course of treatment, particularly when started at a young age in a child's life, is linked to fewer medical visits and less suffering. The study also highlights the poor use of HU in children among SCA, highlighting the necessity of measures aimed at improving both the administration and adherence to this treatment. To improve the overall care of SCA in children, this study offers insightful information about the benefits of HU while highlighting the significance of removing obstacles to its implementation in clinical practice.[49] Belini Junior *et al*. 2015 observational study from Brazil emphasizes the benefits of HU for SCD patients. To summarize, the research indicates that the administration of HU treatment results in several hematological enhancements, such as elevated levels of Hb and HbF production, as well as favorable modifications to blood parameters. In addition, HU is linked to a drop in the frequency of excruciating crises and a reduction in a severity score based on clinical characteristics. These results highlight the potential advantages of HU in improving SCD patients' health-related quality of life and lowering problems associated with their condition in the

Brazilian setting.[50] 2018 study conducted by Di Maggio *et al*. This study emphasizes the benefits of long-term HU treatment for Yemeni sickle-beta-thalassemia patients. The results highlight the advantages of this treatment, which include a lower risk of serious side effects such as ACS and cerebrovascular stroke, a decrease in the frequency of VOC, a decreased need for blood transfusions, and a lower rate of hospitalizations. Furthermore, the administration of HU resulted in elevated levels of Hb and a higher proportion of HbF, both of which suggest better disease control. In this particular population, HU appears to be a viable therapeutic choice for improving quality of life and lowering problems in sickle-beta thalassemia patients.[51] Karimi *et al*. conducted a study in 2012. The beneficial effects of HU treatment on people with β-thalassemia are skillfully highlighted, underscoring the significance of genotype-phenotype considerations and consistent monitoring for efficient disease management. The present investigation enhances our comprehension of the potential advantages of HU as a therapeutic intervention for β-thalassemia, specifically concerning the Iranian populace.[52] According to a 2019 retrospective review conducted in Nigeria by Aikhionbare *et al*., children with SCD who receive HU therapy have a significant reduction in several disease-related complications, such as abnormalities related to Transcranial Doppler (TCD), VOC, stroke, splenic sequestrations, blood transfusions, and hospital admissions. In addition, this medication improves laboratory indicators including PCV and decreases WBC and absolute neutrophil count (ANC). In conclusion, HU therapy seems to be able to improve laboratory parameters and lessen clinical manifestations in these kids, thus enhancing their quality of life and lessening the effects of SCD.[53] Cohort research was carried out in Greece in 2015 by Papadopoulou *et al*. In conclusion, this study shows that HU therapy is safe and effective for treating sickle/beta-thalassemia in children and adolescents. During 2 years, the medication increased vital blood parameters such as Hb, HbF, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) while decreasing pain crises and hospitalization rates. Reticulocyte count, platelet count, WBC count, and bilirubin levels were also decreased. When they did occur, adverse effects were usually dose-dependent and transient. This study concludes that HU is a good therapeutic option for patients with sickle/beta-thalassemia and can be used safely and effectively in these patients.[54] A pilot research focused on the use of HU in children among SCD aged 2–5 years was carried out in the USA in 2000 by Hoppe *et al*. In conclusion, our pilot trial showed that treating young SCD patients with HU is both safe and successful. Hospitalization rates were decreased, total and HbF levels increased, and there were no toxicological side effects from the medication. Crucially, there was no negative impact on the kids' growth and development. These results imply that HU may be a beneficial therapeutic option for this particular age group, with the possibility to enhance their overall health and well-being.[55] The 2000 study by Tshilolo *et al*. which was reported a clinical trial that examined the use of HU in children in sub-Saharan Africa who had SCA. In conclusion, this clinical study showed that treatment with HU raises Hb and Hb levels in fetuses. As a result, there was a decrease in the frequency of painful crises, a decrease in the incidence of nonmalarial infections, a decrease in the requirement for blood transfusions, and a decrease in the death ratio. In the setting of Sub-Saharan Africa, these results demonstrate the beneficial effects of HU in enhancing the health and health-related quality of life of children with SCA.[56] The BABY HUG trial, which Wang *et al*. undertook in 2011, is a randomized controlled experiment that was undertaken in the United States of America. In conclusion, this study showed that treating very young children with sickle-cell anemia with HU is successful. ACS episodes, hospitalization rates, and the requirement for blood transfusions all decreased as a result. Hb and HbF levels increased as a consequence of the treatment. Although there was some mild to moderate neutropenia, overall tolerance was high. According to these results, HU may be a good choice for treating SCA in young children, with possible advantages for their overall health and well-being.[57] The 2012 study by Thornburg *et al*. was a randomized, placebo-controlled, and double-blind trial that was done in the United States as part of the BABY HUG trial. In conclusion, this study showed that treating sickle-cell anemia in very young children with HU improved clinical outcomes. ACS, dactylitis (painful swelling of the hands or feet), hospitalization, and the requirement for blood transfusions all decreased as a result. Crucially, HU was linked to no significant negative consequences. These results demonstrate the advantages of HU use in this particular demographic, enhancing their quality of life and lowering the incidence of problems associated with the condition.[58] In the USA, a randomized, placebo-controlled, double-blind, and clinical trial was carried out in 2014 by Lederman *et al*. In conclusion, the immunologic effects of HU in children among SCA were the main focus of this experiment. The study discovered that treatment with HU resulted in a drop in CD4 and memory T cell counts in addition to a decline in total lymphocyte numbers. Effective immunization could still be obtained in the patients on HU despite these immunological alterations. Crucially, the research found that HU had no negative effects on SCD patients' immune systems. These results are noteworthy because they allay worries regarding possible immunological reactions to HU therapy in this particular patient group.[59]

The 2014 study conducted by Rana *et al*. in the USA was a randomized, double-blind, placebo-controlled, and clinical trial. This research focused on assessing the influence of HU on the growth of young children with SCD. In summary, the study observed that patients treated with HU exhibited a higher baseline BMI score and also had higher weight z-scores compared to the placebo group. Furthermore, the research indicated that an elevated WBC count, reticulocyte count, and ANC were correlated with impaired growth in these children. Importantly, the study demonstrated that the use of HU led to achieving normal or near-normal anthropometric

measurements during the research period. These findings imply that HU treatment can positively affect the growth and development of young child with SCD, offering a valuable option to enhance their overall health and well-being.[60] Patients with the Indian haplotype of SCD responded well to HU treatment, as shown by a 2009 clinical trial conducted in India by Italia *et al*. Within weeks, there was a considerable decrease in the requirement for transfusions, which resulted in improved clinical outcomes as well as less discomfort and exhaustion. HU decreases the overall burden of disease while also improving the health-related quality of life for patients. The study also discovered that greater Hb levels were correlated with increased gamma-globin gene mRNA levels, suggesting that HU therapy may have advantages.[35] The 2018 retrospective study by Estepp *et al*., conducted in the USA, explored the pharmacokinetics of hydroxycarbamide (HU) in children with SCA who received either first-dose or chronic therapy. The study included patients aged 2–17 years who had been on HU treatment for more than 3 months. The research found that in children, weight-normalized peak and plasma concentrations of HU were lower. It also revealed that HU has a rapid rate of absorption, which remains consistent regardless of the duration of therapy. The weight-normalized peak parameter suggested that HU clearance is lower in children who receive chronic dosing. These findings contribute to our understanding of HU pharmacokinetics in pediatric patients with SCA, providing valuable insights for optimizing dosing strategies.[61] In a 2014 study, Polish researchers Wiczling P and associates looked into the HU pharmacokinetics in young SCD patients. They discovered that determining drug exposure (AUC) may be done efficiently with a single plasma concentration measurement taken 15 h after the dose. The kidneys excrete half of the HU dose in its parent form, which provides insight into how the medication is eliminated. Furthermore, the study found that the concentration of HU at 1.5–2 h following oral dose is a trustworthy indicator of systemic drug exposure, which can help with dosing plans for young SCD patients.[62] The effects of HU on children with SCA were assessed in the 2020 prospective cohort study carried out in India by Barma *et al*. The study concluded that HU therapy enhanced the children's quality of life by reducing painful episodes and VOC by 50%. Furthermore, there were significant elevations in MCV, MCH, mean corpuscular hemoglobin concentration, HbF, and total Hb. The study provides hope for improved disease management and improved well-being in this population by confirming the efficacy of the normal therapeutic dose of HU in Indian children with SCA.[63] The 2019 prospective cohort study by Thomas *et al*., which was carried out in the USA, provides important new information about how HU treatment affects children with SCD who have had the condition since infancy. The study concluded that HU therapy significantly improved the children's clinical results in a preventative manner. ACS, pain bouts, blood transfusion requirements, and hospital stays were all considerably decreased. Interestingly, there were no pain episodes that needed to be treated by a doctor. These results highlight how amazing HU is at stopping new problems and enhancing the general health and well-being of children with SCD who begin treatment at a very young age.[64] In 2016, Anders *et al*., carried out a cohort research in New York State, USA, examining the usage of HU in young children diagnosed with SCA. In conclusion, the study shows that HU is thought to be a crucial element for enhancing outcomes in people with SCA, including kids as young as 10–48 months old. The results highlight how critical it is to use HU as a treatment option to improve these young patients' quality of life and illness management. To improve outcomes, this research backs up the early use of HU in children with SCA.[65] In the USA, HU therapy was assessed in a 2017 retrospective study conducted by Quarmyne *et al*. for children and adolescents with SCA. The study discovered that HU significantly improved health-care utilization, resulting in fewer hospitalizations and pain occurrences. ACS, ER visits, and blood transfusions were all less common, and WBC counts were also decreased. Younger children benefited more from HU, according to this study, which validates the treatment's efficacy in juvenile SCA patients and highlights the significance of starting HU therapy early for better clinical results in this population.[66] Bahraini SCD patients receiving HU therapy in the United States were the subject of a 2016 cohort research conducted by Shome *et al*. According to the study, compared to HU non-users, there was a significant improvement in clinical outcomes and a lower hospitalization rate. This emphasizes how important it is to use HU as the main strategy for preventing recurrent hospital stays in children with SCD, as this will improve their quality of life and illness management in the long run.[67] The 2007 Oman study by Zimmerman *et al*. examined the impact of HU treatment on SCA in pediatric patients. Patients receiving either low-dose or high-dose HU between the ages of 2 and 16 were enrolled in the retrospective non-randomized controlled trial. TCD flow velocities did not significantly differ between the two groups in the study, suggesting that low-dose HU was equally effective as high-dose HU. Significantly, the study found that patients with neutropenia could safely receive low-dose HU. These results indicate that HU can assist in lowering TCD flow velocities and potentially lower the risk of cerebrovascular consequences for children patients with severe SCD. It is a safe and effective therapy alternative.[68] The 2010 study by Quinn *et al*. in the USA is a clinical trial that focused on the effects of HU treatment on adolescents and children with SCD. The trial, which extended over 27 years, revealed several key findings. Patients treated with HU experienced a substantial 80% decrease in ACS and a reduction in hospitalizations for painful events, such as splenic sequestrations and progressive osteonecrosis. The study also noted that HU treatment did not impact linear growth but resulted in increased MCV and HbF levels. However, the question of which pediatric patients with SCD should receive HU remains a topic for further investigation. Overall, the study highlights the potential of HU in improving the clinical outcomes and health-related quality of life for children and adolescents with SCD.[69]

Numerous international studies have explored the effectiveness of HU in the treatment of SCD and related conditions. These investigations collectively highlight the potential of HU to mitigate the painful crises and complications associated with SCD, while also underscoring the importance of careful monitoring and dose adjustments to manage potential side effects. In a 2020 Nigerian study, HU emerged as an effective means to reduce painful crises in children with SCD. This was mirrored in a 2006 French study, which suggested that long-term treatment with HU led to fewer VOC in children. However, it was noted that hypersplenism could occur, emphasizing the need for vigilant monitoring. Indian studies from 2009 to 2012 indicated that HU could potentially improve the health-related quality of life for SCD patients, especially those with high levels of HbF and certain hereditary factors. These findings are supported by a 2015 Iranian cohort study, which demonstrated that HU treatment could decrease spleen size, lower hospitalization rates, and reduce the need for blood transfusions. Moreover, a 2005 U.S. clinical trial showed that newborns with SCD could safely benefit from long-term HU treatment, leading to improved growth rates and better spleen function. The HOPS trial in 2020 emphasized the importance of determining the ideal dosage and timing of HU treatment, with the potential to significantly improve the health-related quality of life and overall health of SCD patients. The 2013 U.S. retrospective study indicated that HU treatment improved survival rates and reduced disease severity in children with SCD, primarily due to a decrease in infections and ACS. Additional studies reinforced the benefits of HU therapy, including a 2009 U.S. prospective pilot trial that demonstrated its tolerability in young children with SCD, a 2015 Indian study revealing increased HbF levels and reduced hemolysis, and a 2005 Belgian retrospective study highlighting the reduction of cerebrovascular accidents in high-risk SCD individuals. A 2015 Portuguese study showcased how HU reduced the need for transfusions, hospital admissions, and VOC, raised HbF levels, and had no significant negative impact on children and adolescents with SCD. A 2019 retrospective study emphasized the importance of improving administration and adherence to HU treatment, as it led to fewer medical visits and less suffering in children with SCD. Further investigations expanded the scope of HU's benefits to related conditions. A 2018 study focused on the treatment's advantages for Yemeni patients with sickle-beta thalassemia, highlighting a lower risk of serious side effects, reduced crisis frequency, and a decreased need for blood transfusions. Another 2012 study underscored the potential advantages of HU as a therapeutic intervention for β-thalassemia, particularly among the Iranian population. Finally, a 2019 retrospective review in Nigeria confirmed that HU therapy led to significant reductions in disease-related complications, improvements in laboratory indicators, and enhanced quality of life for children with SCD. In addition, a 2015 cohort study conducted in Greece found that HU therapy was safe and effective for treating individuals with sickle/beta-thalassemia. Collectively, these studies suggest that HU holds promise as a treatment option for a range of hemoglobinopathies and emphasizes the need for careful management and further research to optimize its use.

CONCLUSION

This comprehensive review of multiple studies spanning different geographical regions and patient populations underscores the versatility and potential benefits of HU as a therapeutic intervention in the management of SCD and related conditions. The research collectively highlights the capacity of HU to reduce painful crises, lower disease-related complications, improve hematological parameters, and enhance the overall quality of life for affected individuals, regardless of their age or specific SCD subtypes. While these findings offer substantial promise for the broader utilization of HU, they also underscore the need for meticulous monitoring and individualized treatment regimens. The abundance of evidence within this review supports the notion that HU holds considerable potential in revolutionizing the care and well-being of SCD patients, emphasizing its pivotal role in mitigating the burdens of this debilitating condition and the necessity for continued research and optimized clinical implementation.

Implication of study

The comprehensive review of HU treatment for SCD reveals its promising potential to alleviate the suffering and complications associated with SCD across diverse patient populations. This review underscores the pressing need for standardized protocols and guidelines for the administration of HU, as its efficacy and side effects can vary among individuals. The collective evidence strongly encourages further research to corroborate its benefits in a larger, more comprehensive manner, helping to establish HU as an essential component of SCD management. In addition, the reviewed studies suggest potential applications of HU in other Hb disorders, extending its utility and underscoring its importance in the broader field of hematology. Thus, the implications of this review emphasize the crucial role HU can play in improving the lives of those afflicted with SCD and related conditions when administered in a personalized and monitored manner.

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ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

PATIENT CONSENT

Not Applicable.

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