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Systematic Review

The Indian experience with hydroxyurea in sickle cell disease: A 25-year systematic review

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***Background & objectives*: Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the β-globin gene, leading to the production of abnormal haemoglobin and the deformation of red blood cells into a sickle shape. This results in serious complications, including vaso-occlusive crises (VOC), chronic anaemia, infections, stroke, acute chest syndrome, delayed growth, and multi-organ damage. SCD poses a significant public health burden in India, particularly among tribal populations. Hydroxyurea (HU) is a disease-modifying therapy known to increase foetal haemoglobin (HbF) levels and reduce SCD-related complications. This review aims to evaluate the efficacy and safety of HU in Indian SCD patients.**

***Methods*: A systematic review of 27 Indian studies (involving 3,817 patients with SCD), published between January 2000 and August 2024, was conducted. Studies were sourced from major databases, and included clinical trials, prospective and retrospective studies, and observational cohorts. Key outcomes assessed were HbF levels, VOC frequency, transfusion requirements, hospitalisations, and adverse effects.**

***Results*: HU significantly increased HbF levels (10.9-77.3%), reduced VOC frequency by 79-93 per cent, and lowered transfusion needs by 50-85 per cent. Hospitalisations and anaemia also improved. HU was generally safe, with mild, reversible side effects like neutropenia and thrombocytopenia in few cases.**

***Interpretation & conclusions*: HU is effective and well tolerated in Indian patients with SCD.**

Key words Blood transfusion - haemoglobinopathy - hydroxyurea - sickle cell disease - sickle cell anaemia - vaso-occlusive crises

Sickle cell disease (SCD) is a haemoglobinopathy caused by a mutation in the β-globin gene, leading to production of sickle haemoglobin (HbS)[1]. When deoxygenated, HbS polymerises, distorting red blood cells into a sickle shape, resulting in vaso-occlusion and haemolyticanaemia[2]. Globally, about 7 per cent of people carry abnormal Hb genes[3].

In India, SCD prevalence is estimated at 1.17 per cent overall, with 4.05 per cent among tribal populations and 0.84 per cent among non-tribal groups. The burden is higher in Madhya Pradesh, Odisha, Chhattisgarh, Gujarat, and Maharashtra, making it a significant public health challenge[4].

Historically, SCD treatment options were limited. Advances in molecular biology and supportive regulatory policies have introduced new therapies. FDA-approved drugs include hydroxyurea (HU), L-glutamine, crizanlizumab, and voxelotor. However, the cost of newer therapies restricts access in low resource settings[5]. Bone marrow transplantation is considered for high-risk patients, and recently approved gene therapies offer potential cures, with financial barriers[6]. HU was initially approved by the US-FDA in 1967 for chronic myeloid leukaemia and squamous cell carcinoma of head and neck[7]. HU tablets were later approved for SCD by the US-FDA (1998) and EMA (2007). In India, it was used off-label until December 2021, when CDSCO approved 500 mg HU capsules for sickle cell anaemia (SCA), driven by the CSIR-SCA Mission and Cipla[7].

The clinical efficacy of HU in SCD is primarily attributed to its ability to increase HbF, reducing HbS concentration and polymerisation, which lowers haemolysis and increases total Hb concentration[8]. Over 25 yr, HU has reduced the frequency and severity of painful episodes by 50 per cent and decreased the incidence of acute chest syndrome (ACS) and blood needs by around 50 per cent in adults[9]. It is recommended for patients with repeated ACS or more than three hospitalised crisis per year.

Approved by USFDA, EMA, and CDSCO, HU remains a cornerstone of management of SCD[9]. This systematic review is aimed at evaluating the efficacy and safety of hydroxyurea in Indian patients with SCD.

Materials & Methods

Search strategy: An extensive literature search was conducted using online databases *viz*. PubMed Central, ScienceDirect, PubMed (Medline), and Cochrane Library, to identify pertinent studies. Keywords used in the search included 'hydroxyurea', 'hydroxycarbamide', 'sickle cell disease','sickle cell anaemia','India', and their combinations. The studies search covered the period from January 2000 to August 2024.

Inclusion and exclusion criteria: The search results were screened based on the predefined inclusion and exclusion criteria. Included in the review are prospective and retrospective studies, observational cohort studies, descriptive studies, and randomised placebo-controlled clinical trials that documented the efficacy and safety of HU in the management of SCD in the Indian population. Conference papers, letters, drug profiles, reviews, and meta-analyses as well as studies involving the use of HU for conditions other than SCD were excluded. Studies involving children under two yr of age were also excluded, in line with the NSCEM guidelines, which do not recommend HU for this age group. Only studies written in English and published in peer-reviewed journals were considered.

Data extraction: The title and abstract of the studies were scrutinised by the authors, and the final selection of articles was made through mutual consensus. A reviewer was consulted in the event of disagreement amongst the authors. Journal status, publication year, study design, methodology, objectives, and outcome results, were systematically extracted from the selected articles. In addition to the efficacy outcomes, data on mean baseline and follow-up levels of Hb, mean corpuscular volume (MCV), and absolute neutrophil count (ANC) were recorded. Information on the frequency and type of adverse effects reported in individual studies was systematically retrieved to evaluate the safety profile of HU.

Results

A preliminary search of various electronic databases using the defined keyword combinations (as mentioned in 'search strategy') identified 4,995 studies - primarily from PubMed Central (n=3,522), followed by ScienceDirect (n=1,129), PubMed (n=330), and the Cochrane Library (n=14). After removing 3,928 duplicates, 1,067 unique articles were screened. Based on titles and abstracts screening, 948 were excluded as irrelevant, leaving 119 articles for full-text review. Following evaluation against predefined inclusion criteria, 27 studies were included for the systematic review. The screening and selection process is illustrated in figure.

The selected 27 studies are outlined in table. The studies were assessed for the efficacy and safety of HU in managing SCD across diverse patient groups and dosing regimens[10-36]. These comprised 17 prospective (cohort, observational and longitudinal), four retrospective studies, one ambispective (retrospective and prospective) study, three randomised controlled trials, and two observational studies collectively involving 3,817 SCD patients from various clinical settings in India.

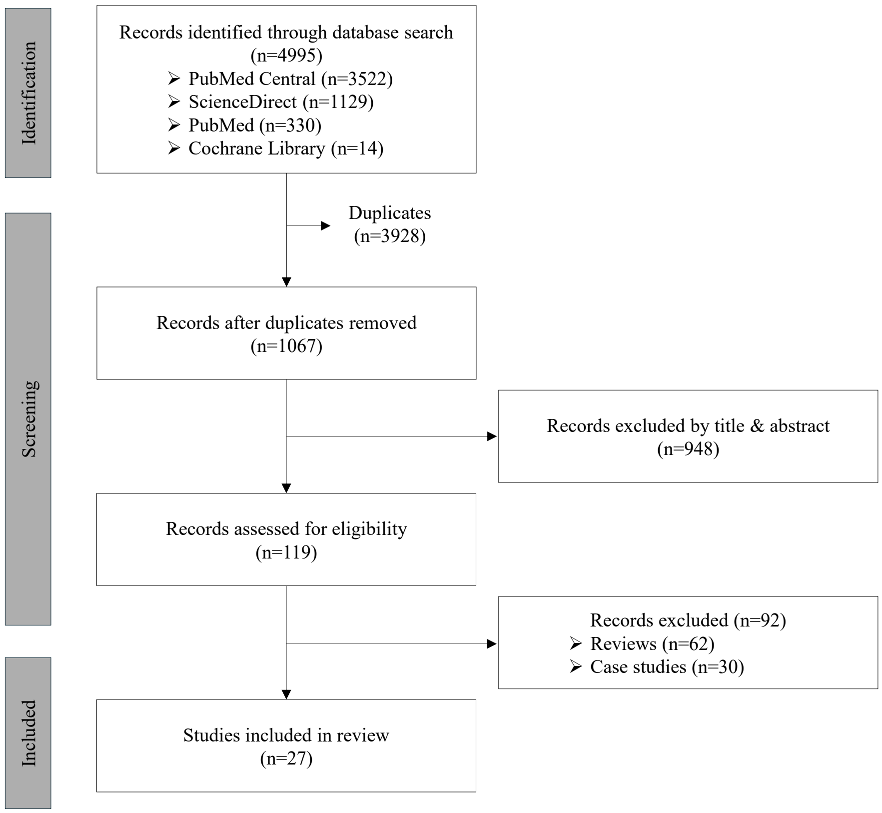

Figure. Selection of pertinent studies for systemic review as per PRISMA guidelines.

Participants ranged in age from 1- 60 yr. Although patients below two yr were generally excluded, one study (age range 1 to 18 yr, mean age 7.69$\pm$3.43 yr) was included due to its valuable insights into HU efficacy in young children[27]. Eight studies focused on paediatric population (<18 yr)[11,12,15,18,25,27,30,35], five on adults (>18 yr)[10,17,23,24,32], and 12 included both age gro ups[10,11,13,14,16,18,21,22,26,28,33,34]. Two studies did not specify age[21,31]. Most studies have a follow up duration of 12 to 24 months, allowing for medium-term evaluation, while a few extended up to 36 months for long-term assessment[17,22,32,34].

HU doses ranged from 10 to 30 mg/kg/day. Seven studies[10-12,15,30,33,34] used a fixed low dose of 10 mg/kg/day without escalation, whereas five studies[13,17,22,23,27] adopted a dose-escalation approach, starting at 15 mg/kg/day and increasing by 5 mg/kg/day every four weeks if no clinical or haematological response was observed[27].

HU efficacy:

Effect on VOC, blood transfusions and hospitalisation: Low-dose HU (10 mg/kg/day) has shown significant efficacy in reducing VOC, blood transfusion, and hospitalisations. In studies by Italia *et al*[10,18], there were significant increases in HbF levels ranging from 16.9 per cent to 77.3 per cent (*P*< 0.001 in both studies), contributing reduced VOC and related complications. Similarly, Pradhan *et al*[12], reported a 10.9 per cent rise in HbF (12.5% to 23.4%; *P*<0.001), significantly reducing transfusion requirements. Patel *et al*[11], documented a 93 per cent reduction in VOC episodes (from 6.43 to 0.43/yr; *P*< 0.001). Similarly, Sethy *et al*[15] reported complete resolution in 92 per cent of patients (*P*< 0.01). Pondugala *et al*[27], also noted a sharp drop in VOC episodes (from 5.7±1.44 to 0.57±0.68/yr; *P*< 0.001).

HU significantly reduced blood transfusion requirements. Somkuwar *et al*[35], observed a decline from 1.88 to 0.3 transfusions/year (*P*<=0.001), and Gupta *et al*[16] reported a drop from 5.36 to 0.32/yr (*P*<0.001), reflecting an 84-94 per cent reduction.

In addition to increasing HbF and reducing VOC and blood transfusions, HU therapy showed improvements in other efficacy parameters like total Hb across multiple studies. Italia *et al*[10], found Hb levels increased from 7.6 to 9.2 g/dL (*P*< 0.001), while Pradhan *et al*[12], reported a rise from 6.78 to 8.42 g/dL

Table. Characteristics and key outcomes of studies extracted for the systematic review

Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Italia *et al*[10] 2009	Mumbai & Nagpur, India	Prospective cohort, evaluate the efficacy and safety of HU in Indian SCD patients N=77	≥5 VOC/yr, CNS or chest syndrome, avascular necrosis	Inability to adhere to follow ups	Group I (18-35 yr), Group II (5-17 yr), Group III (18-35 yr)	10-15 mg/kg/day of HU	24 months	78% had no further crisis; significant HbF increase (P<0.001) 91% stopped blood transfusions; significant Hb increase (P<0.001)	1 case of leucopoenia
Singh *et al*[14] 2010	Chhattisgarh, India	Prospective, Evaluate the efficacy of HU in SCD patients in reducing crisis & hospital admissions. N=27 enrolled N=24 completed	Homozygous SCD with ≥3 hospitalisations/yr, stroke, acute chest syndrome, Hb<7 g/dL	Pregnancy, active liver disease, prior HU treatment, non-compliance	Mean 19.85 yr	20-25 mg/kg/day	1 yr	Significant increase in HbF% from 12.83% to 19.17% (P=0.01). Mean hospital admissions reduced from 4.75 to 2.25 (P=0.03) Mean number of crisis reduced from 3.63 to 1.67 (P=0.008) Increase in MCV from 82.57 fL to 89.87 fL (P=0.0045)	Mild, reversible bone marrow suppression in ~5% of patients; neutropenia (recovered in 1 week)
Jain *et al*[25] 2012	Nagpur, India	Double-blind randomised controlled trial, evaluate the efficacy and toxicity of low fixed-dose HU in Indian children with severe SCDN=60 (30 in HU group, 30 in placebo group)	Severe SCD (VOC >3/yr or transfusions >3/yr)	HIV positivity, chronic illness	5-18 yr	10 mg/kg/day	18 months	Hb increased from 8.10±0.68 to 9.29±0.55 g/dL (P<0.001) HbF increased from 19.80±6.90% to 24.00±5.90% (P<0.001) Significant reduction in VOC, blood transfusions, and hospitalisations (P<0.001)	Mild (nausea, skin rash); no significant leukopenia, neutropenia, thrombocytopenia, or organ toxicity
Jain *et al*[36] 2012	Nagpur, India	Retrospective analysis, to assess the clinical course & severity of sickle cell anaemia (SCA) in children from Central India. N=316	SCA confirmed; children <18 yr; follow up ≥1 yr	Not explicitly stated	Median age 3.84 yr (range 15 days to 16 yr)	Not mentioned (focus on clinical presentation before HU initiation)	5.8±5.7 yr of follow up	1015 blood transfusions (55.4 per 100 person-yr)793 VOC episodes (43.3 per 100 person-yr)175 episodes of severe infection (9.5 per 100 person-yr)96 patients (30%) had severe disease	Not mentioned (focus on disease severity & clinical events)

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Patel *et al*[11] 2012	Orissa, India	Prospective observational study, to assess the efficacy of low-dose HU (10 mg/kg/day) in reducing painful crisis and blood transfusion requirements in SCA patients. N=118 (27 paediatric, 91 adults)	SCA patients with >3 painful crisis/yr or >2 blood transfusions/yr	Other sickle cell syndromes, age <3 or >60 yr, poor follow up compliance, previous HU treatment <80% compliance	Paediatric: 3-14 yr, Adult: 15-45 yr	10 mg/kg/day	24 months	71.5% of paediatric patients and 92.2% of adults had a >50% reduction in painful crisis (P=0.008) 95% of patients became transfusion-independent HbF increased from 19.0% to 22.5% in paediatric and from 18.2% to 22.5% in adults (P<0.0001)	7.5% had mild, transient bone marrow suppression, no major hepatic or renal toxicity
Pondugala *et al*[27] 2012	Andhra Pradesh, India	Single-blind randomised controlled trial, to assess the efficacy of HU in increasing HbF and reducing VOC and transfusions in children with SCD. N=60 (30 in HU group, 30 in placebo group)	SCD patients with HbS and >2 VOC in the past yr	Not explicitly stated	1-18 yr	15 mg/kg/day, increased by 5 mg/kg/day if no response	12 months	VOC reduced from 5.7 to 0.57 (P<0.001). Blood transfusions reduced from 2.9 to 0.3 (P<0.001) HbF increased from 28.38% to 39.77% (P<0.001) MCV increased from 76.32 to 93.63 fL (P<0.001)	Mild reversible bone marrow suppression (WBC reduced from 11,546 to 8,023; P<0.001) Reticulocyte count reduced from 2.33% to 0.89% (P<0.001)
Italia *et al*[18] 2013	Mumbai, India	Prospective observational, to compare the response to HU *in vitro* & *in vivo* in patients with different haemoglobinopathies by measuring HbF and γ-mRNA expression. N=24	Severe hemoglobino-pathies, including SCD & β-thalassemia, with >5 episodes of VOC annually or frequent transfusions	Not explicitly mentioned	5-30 yr	10-15 mg/kg/day	24 months	57.7% responders had no further crisis or transfusion needs, with a 63.8% increase in F-cells and a 205.5% increase in γ-mRNA expression (P<0.01). Partial responders (19%) showed a 50% reduction in transfusion requirements, with a 61.2% increase in F-cells & a 21% increase in γ-mRNA expression (P<0.01)	2 patients experienced neutropenia (HU was stopped temporarily)

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Jain *et al*[30] 2013	Nagpur, India	Prospective longitudinal study, to evaluate the efficacy of low fixed-dose HU (10 mg/kg/day) in children with sickle cell anaemia (SCA), N=144 children	SCA with ≥3 episodes of VOC or transfusions, or acute chest syndrome/ stroke	Pregnancy, HIV, abnormal renal or liver function	3.5-17.9 yr (mean age 13.8 yr)	10 mg/kg/ day	24 months	VOC reduced by 96.4% (P<0.001). Blood transfusions reduced by 79.3% (P<0.001) Hospitalisations reduced by 93.5% (P<0.001) Hb increased from 8.53 to 9.66 g/dL (P<0.001) HbF increased from 16.45% to 21.98% (P<0.001)	21 episodes of laboratory toxicity (neutropenia, thrombocytopenia, abnormal liver and kidney function) leading to temporary HU withdrawal (P values not provided for adverse events)
Oberoi *et al*[23] 2014	Chandigarh, India	Retrospective analysis, to describe the clinical and haematological profile of HbSD-Punjab patients from North India, N=10	Patients diagnosed with HbSD-Punjab using HPLC & confirmed *via* molecular analysis	Not explicitly mentioned	Median age at symptom onset 3.5 yr (range 1.9 to 7.2 yr)	15-22 mg/ kg/day	Median 7 months (range 6 to 45 months)	Reduction in painful VOC: decreased from 2-3 episodes/yr to 0-1/yr (in patients receiving HU) Hb increased from 6.8 to 9.3 g/ dL (P value not provided)	One patient developed transient neutropenia
Patel *et al*[24] 2014	Odisha, India	Prospective cohort study, to evaluate the efficacy of HU in reducing VOC & blood transfusion requirements in HbSD-Punjab patients, N=20 in the HU group, 17 in the non-HU group	HbSD-Punjab patients with ≥3 episodes of VOC or ≥2 transfusions in the last 12 months	Not explicitly mentioned	1-45 yr (mean 21.5 yr)	10 mg/kg/ day	24 months	VOC reduced from 3.52 to 0.4 episodes/yr (P<0.0001) Blood transfusion reduced from 1.44 to 0.02/yr (P=0.0007) HbF increased from 17.3% to 21.2% (P<0.0001) Hb increased from 8.02 g/dL to 9.8 g/ dL (P<0.0001) Significant reduction in WBC count, platelet count, total serum bilirubin, and LDH levels	No significant myelotoxicity, renal, or hepatic toxicity observed
Deshpande *et al*[13] 2016	Gujarat, India	Single-centre observational study, to evaluate the effects of HU on pain episodes, transfusion requirements, and haematological parameters in SCD patients, N=70	HPLC-confirmed SCD patients of all ages	Not explicitly mentioned	0-45 yr (various age groups)	15-30 mg/ kg/day	12 months	Significant reduction in pain episodes across all age groups (P<0.0001) HbF levels increased significantly across all age groups (P<0.0001) Blood transfusion requirement decreased, significant in the 11-20 yr group (P=0.008) Hb increased significantly, particularly in the 21-30 yr group (P<0.001)	Mild decrease in WBC & platelet count, but not statistically significant

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Mohanty *et al*[33] 2017	Odisha, India	Retrospective study, to evaluate iron load* & its correlation with transfusion frequency and haemolytic parameters in SCA (HbSS) patients, N=208*. While HU was not the primary intervention studied, it was part of the therapeutic regimen	Adult SCA patients with HbSS & no comorbidities affecting iron load	Double heterozygous states or other hemoglobino-pathies	18-48 yr	20 mg/kg/day	5 yr	9.6% of patients had iron overload (serum ferritin >1000 ng/ml, P<0.001) 80.8% had normal or borderline iron levels (P<0.001) Transfusion frequency positively correlated with iron overload (P<0.001) Haemolytic parameters and serum hepcidin levels had no significant correlation (P=0.0634)	Not mentioned
Sahoo *et al*[34] 2017	Odisha, India	Prospective observational study, to evaluate the impact of HU on seminal fluid parameters and fertility in male SCD patients, N=100 (50 without HU and 50 with HU)	Male SCD patients with ≥3 VOCs/yr or ≥2 blood transfusions/yr	Patients with HbS/ß-thal, HbS/HbD Punjab, HbS/HbC, or refusal of consent	18-45 yr	10 mg/kg/day	26 months	Sperm concentration reduced from 54.28±16.2 million/ml to 39.26±29.32 million/ml during HU therapy (P<0.0001) Oligospermia developed in 20% & azoospermia in 10% of patients during HU therapy 73% of patients with altered sperm parameters recovered after stopping HU for 3 months	Significant decrease in sperm concentration, motility, & morphology during HU therapy (P<0.0001)
Pradhan *et al*[12] 2018	Odisha, India	Prospective observational study, to evaluate the effect of low-dose HU (10 mg/kg/day) on clinical & haematological parameters in SCD patients, N=100 (31 paediatric, 69 adult)	HbSS patients with frequent VOC (>3/yr), transfusions (>2/yr), or acute chest syndrome (≥1 episode/yr)	HbS/ß-thal, HbSC, HbS-SD Punjab, pregnancy, severe hepatic or renal impairment	Paediatric: 8.47±4.1 yr; Adult: 25.9±8.2 yr	10 mg/kg/day	24 months	VOC reduced by 79.6% in paediatric (P=0.0001) & 64.1% in adult patients (P=0.0001) Blood transfusion reduced by 85.2% in paediatric (P=0.0001) & 85.9% in adults (P=0.0001) HbF increased by 13.7% in paediatric (P=0.0001) & 23.8% in adults (P=0.0001) Hb increased by 25% in paediatric (P=0.0001) & 31.7% in adults (P=0.0001)	Mild myelotoxicity (decreased ANC, TPC, WBCs), reversible in 36 patients (paediatric: 8; adult: 28)

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Sethy *et al*[15] 2018	Odisha, India	Prospective study, to evaluate the efficacy & safety of low fixed-dose HU (10 mg/kg/day) in reducing VOC and transfusion requirements in adult HbSS patients, N=128 (82 males, 46 females)	Adult HbSS patients with >2 VOCs/yr or transfusion need of 1-2 units/month	Pregnancy, HIV infection, severe hepatic or renal impairment	18+ yr	10 mg/kg/day	12 months	VOC reduced by 92% ($P<0.001$). Blood transfusions reduced by 87% ($P<0.001$). Significant increase in Hb (from 8.42 g/dL to 9.78 g/dL, $P<0.001$) HbF increased slightly (from 18.06% to 21.66%, $P > 0.05$) Significant reductions in TLC, TPC, S. Bilirubin, and S. LDH ($P<0.001$)	Mild & transient neutropenia (3 cases), thrombocytopenia (2 cases), and hepatic or renal dysfunction (6 cases total), all reversible
Warang *et al*[22] 2018	Mumbai, India	Observational study, to investigate the role of the ubiquitin-proteasome system (UPS) dysfunction and its association with oxidative stress in SCD patients & the impact of hydroxycarbamide (HC) therapy, N=44 SCD patients (27 treated with HC & 17 untreated) & 55 healthy controls	SCD patients (HbSS genotype), aged 11-50 yr	Recent blood transfusion within 3 months of study enrolment	11-50 yr	Not specified (patients were on HU for 2 yr)	3 yr	SCD patients had elevated polyubiquitinated proteins and increased oxidative stress ($P<0.001$) Hydroxycarbamide (HC) therapy significantly reduced reactive oxygen species (ROS) and polyubiquitinated proteins in RBCs of SCD patients ($P<0.001$) HC-treated patients exhibited higher proteasomal activity in all three subunits (b1, b2, and b5) ($P<0.001$)	Not mentioned
Dave *et al*[17] 2019	Gujarat, India	Prospective observational, to assess lost-to-follow-up (LTFU) rates & clinical outcomes in SCD patients registered in an NGO-led SCD programme, N=404	SCD patients registered in the NGO programme, primarily tribal population	Not explicitly mentioned	Mean age 19 yr	Not specified (patients with severe SCD received HU based on clinical need)	18 months with follow up for 30 months	LTFU rate: 21 per 100 person-yr (28% of patients) Significant reduction in pain crisis (from 277 to 53.4 episodes per 100 person-yr, $P<0.001$) Reduction in hospitalisation rates (from 49.8 to 42.2 per 100 person-yr, $P=0.05$) Reduction in blood transfusions (from 27.4 to 17.8 per 100 person-yr, $P<0.001$)	Not mentioned

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Somkuwar *et al*[35] 2019	Maharashtra, India	Prospective longitudinal follow up study, to evaluate the short-term safety and beneficial effects of HU therapy in children with severe SCD (SS pattern), N=40	SCD children aged 5-15 yr with ≥2 acute painful crisis/yr or ≥3 blood transfusions/yr	Children <5 yr, other systemic illnesses, regular use of certain drugs (theophylline, oestrogen, *etc.*)	5-15 yr	10 mg/kg/day	2 yr	Significant reduction in acute painful events (from 2.11 to 0.25 per yr, P=0.001). Significant reduction in blood transfusions (from 1.88 to 0.3 per yr, P=0.001) No recurrence of acute chest syndrome or stroke Significant increase in HbF (from 17.8% to 18.13%, P=0.001)	Nausea (8.33%), diarrhoea (2.78%), haematuria (2.78%) Haematological toxicities: anaemia (13.89%), thrombocytopenia (11.11%), neutropenia (8.33%) Transient renal (11.11%) and hepatic toxicity (8.33%)
Barma *et al*[26] 2020	Odisha, India	Prospective cohort study, to evaluate the clinical & haematological response to HU in children with SCA at a dose of 20 mg/kg/day, N=114	SCA children aged 5-14 yr with severe disease (>3 VOCs/yr or >3 blood transfusions/yr)	Refusal of treatment, active liver/kidney disease, previous HU therapy	5-14 yr	20 mg/kg/day	24 months	VOC episodes reduced by 50% (P<0.01). Blood transfusions reduced by 56% (P<0.01) Hb concentration increased by 52%, HbF increased by 51%, MCV, MCH, and MCHC improved by 7%, 3%, and 2.5%, respectively School attendance and quality of life improved significantly	Two cases of neutropenia and thrombocytopenia, leading to cessation of HU therapy. No other major adverse effects
Soren *et al*[20] 2022	Odisha, India	Prospective observational study, to assess the effect of HU on hospital stay & analgesic utilisation in SCA patients with VOC,N=359 (187 on HU, 172 controls)	Homozygous SCA patients (HbSS) with VOC, aged 15-60 yr	Pregnancy, renal impairment, liver disease, Hb<5 g/dL, ANC <2 × 10^3/µL, platelet count <80 × 10^3/µL	15-60 yr (mean age 27.10±11.29 yr)	10 mg/kg/day	24 months	Reduced hospital stays by 1.4 days (5.16 *vs.* 6.55 days, P<0.001). Reduced analgesic utilisation by 1.18 days (4.8 *vs.* 5.98 days, P<0.001). Lower pain intensity (VAS score: 7.23 *vs.* 7.97, P<0.001) Lower serum LDH levels at discharge (800.05 *vs.* 1257 U/L, P<0.001)	No significant myelotoxicity, neutropenia, or thrombocytopenia

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Gupta *et al*[16] 2023	Madhya Pradesh, India	Ambispective observational study, to assess the impact of HU on blood transfusion frequency, VOC, & hospitalisations in children with SCA, N=190 enrolled, 84 completed follow up	Diagnosed cases of SCD confirmed by Hb electrophoresis	Patients <2 yr, HIV reactive, already on HU before study	1-15 yr (majority aged 6-10 yr)	15-20 mg/kg/day	12 months	Blood transfusion frequency reduced from 5.36/yr to 0.32/yr (P<0.001) VOC frequency reduced from 6.43/yr to 0.43/yr (P<0.001) Hospitalisations reduced from 3.52/yr to 0.13/yr (P<0.001)	No major adverse effects reported, mild neutropenia and thrombocytopenia observed but reversible
Kargutkar *et al*[21] 2023	Mumbai, India	Prospective study, to evaluate the effect of HU on erythrocyte apoptosis & clinical parameters in hemoglobinopathy patients, including thalassemia intermedia, SCA, & HbE-β-thalassemia, N=115 patients (45 thalassemia intermedia, 40 SCA, 30 HbE-β-thalassemia)	Patients with thalassemia intermedia, SCA, or HbE-β-thalassemia	Not explicitly mentioned	Thalassemia intermedia: 6.97±4.9 yr; SCA: 13.8±10.28 yr; HbE-β-thalassemia: 11.33±8.77 yr	10 mg/kg/day	3 and 6 months of follow up	Significant reduction in phosphatidylserine (PS) exposure on erythrocytes after 3 and 6 months of HU therapy in all patient groups (P<0.0001) Increase in HbF levels: Thalassemia intermedia (59.9% to 77.3%), SCA (21.5% to 30.69%), HbE-β-thalassemia (29% to 33.3%) (P<0.001). Reduction in VOC & hospitalisation rates (not specified in detail)	Not mentioned
Kargutkar *et al*[19] 2023	Mumbai, India	Prospective study, to evaluate the role of microRNA in HU -mediated HbF induction in SCA patients, N=30 (baseline), 20 followed up after HU therapy	SCA patients with HbSS genotype	Not explicitly mentioned	Mean age: 14.1±10.5 yr (range 3-38 yr)	10 mg/kg/day	6 months	HbF levels increased from 16.88±3.13% to 30.45±2.5% (3 months) and 35.18±2.93% (6 months) (P<0.0001)Significant upregulation of miR-210, miR-16-1, miR-29a, & downregulation of miR-96 after HU therapy (P<0.0001). Correlation between miRNA expression and HbF induction: miR-210 (r = 0.874), miR-16-1 (r = 0.809), miR-29a (r = 0.856), miR-96 (negative correlation, r = -0.879)	Not mentioned

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Khargekar *et al*[29] 2023	Mumbai, India	Randomised controlled trial, to compare the efficacy & safety of low-dose (10 mg/kg/day) versus standard-dose (20 mg/kg/day) HU in SCA patients in India, N=37 (18 in low-dose group, 19 in standard-dose group)	SCA patients aged 2-14 yr with HbF levels below 15% and clinical severity	Not explicitly mentioned	Mean age 8.9±2.8 yr (low dose) and 8.6±2.5 yr (standard dose)	10 mg/kg/day *vs.* 20 mg/kg/day	6 months	HbF increase: 4.81±2.71% in the standard dose group *vs.* 1.55±2.32% in the low dose group (*P*<0.001) Hb increase: 0.71±0.77 g/dL (standard dose) *vs.* 0.18±0.71 g/dL (low dose) (*P*<0.001). White blood cell (WBC) count and platelet count decreased significantly in both groups, more in the standard dose group (*P*<0.001). No critical clinical events (VOC, stroke, acute chest syndrome) observed during the follow up period	Two patients in the standard dose group developed ANC <1000 requiring temporary cessation of HU therapy
Lad *et al*[28] 2023	Chhattisgarh, India	Prospective observational study, to evaluate the clinical and haematological efficacy & safety of HU in a paediatric cohort of SCD patients, N=164 (138 HbSS & 26 HbS-β-thalassemia)	Paediatric SCD patients (HbSS and HbS-β-thal) with at least 3 months of data before and after starting HU	Recent blood transfusions, comorbidities, or HbSβ+ mutation	≤14 yr (mean age 9.24±3.14 yr)	Mean dose 18.7±7.0 mg/kg/day	24 months	Significant increase in HbF (from 22.26% to 25.58%, *P*<0.001), Hb (from 8.74 g/dL to 9.30 g/dL, *P*<0.001), & MCV (from 85.95 to 91.00 fL, *P*<0.001) Reduction in VOC (from 31.71% to 3.66%, *P*<0.001), pain episodes (from 79.88% to 51.22%, *P*<0.001), & hospitalisations (from 80.49% to 19.51%, *P*<0.001)	No significant adverse effects, including haematological toxicity
HU efficacy in pregnant women									
Patel *et al*[31] 2020	Odisha, India	Retrospective study, to analyse the pregnancy outcomes & associated complications in women with SCD, N=292	Married parous women with SCD visiting the institute during the study period	Refusal to participate, involvement in other trials	Not specified (mean age at first pregnancy: 22.7±3.3 yr)	Not specified (only 15 women received HU pre-conception)	Data from an 8-yr period	73.8% live births 9.3% spontaneous abortions, 6.5% stillbirths, 4.9% neonatal deaths, 2.5% intrauterine deaths 33.3% pregnancies had painful events, 39.3% required blood transfusions 25% caesarean deliveries, 9.6% pre-term births	Not mentioned (focus on pregnancy complications)

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Author, yr	Place of study	Type of study, study design & aim	Inclusion criteria	Exclusion criteria	Age of patients	Dose & dosage of HU	Duration of study	Efficacy	Adverse effects
Daigavane *et al*[32] 2013	Cuttack, Odisha, India	Prospective randomised study, to assess the perinatal outcomes in sickle cell anaemia (SCA) mothers. N=60 pregnant women with SCA	Primigravida, age <30 yr, HbSS genotype, fewer than 3 VOCs/yr	Double heterozygous status, other hemoglobino-pathies, comorbidities	19-29 yr (median 25 yr)	20 mg/kg/day (HU was withheld during pregnancy but reintroduced for severe VOCs)	2 yr	Low birth weight <2500 g in 53.33% of cases (P=0.0003). Preeclampsia in 13.3% of cases (P=0.0063). Perinatal mortality rate of 16.66% (P=0.0002). Preterm birth rate 16.6% (P=0.0087). Neonatal deaths 6.66% (P=0.0185)	VOC in 30% of patients (P=0.0001) Jaundice & pulmonary complications in 10% of cases (P=0.0024). No maternal mortality

SCD, sickle cell disease; HU, hydroxyurea; SCA, sickle cell anaemia; VOC, vaso-occlusive crisis; HbF, fatal haemoglobin; Hb, haemoglobin; HbSS, homozygous sickle haemoglobin; HbS/β-thal, haemoglobin S/beta-thalassemia; HbSC, haemoglobin sickle cell disease with haemoglobin C; HbSD, haemoglobin sickle cell disease with haemoglobin D; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; ANC, absolute neutrophil count; TPC, total platelet count; TLC, total leukocyte count; LDH, lactate dehydrogenase; WBC, white blood cell; HPLC, high-performance liquid chromatography; CNS, central nervous system; UPS, ubiquitin-proteasome system; ROS, reactive oxygen species; miRNA, microRNA; PS, phosphatidylserine; HbE-β-thal, haemoglobin E-beta-thalassemia; VAS, visual analogue scale

(P<0.001), indicating better oxygen-carrying capacity and reduced anaemia.

Effect on haematological parameters: An increase in MCV observed with HU therapy, attributed to macrocytosis and reticulocytosis, reflects its improved erythropoietic response. Pondugala *et al*[27] reported that MCV increased from 76.3 fL to 93.6 fL (P< 0.001) after HU therapy, reflecting improved red cell indices and less haemolysis. Mean corpuscular haemoglobin (MCH), another key marker of RBC quality, also improved with HU. In the study by Pradhan *et al*[12], MCH increased from 22.4 pg to 27.7 pg (P<0.001), indicating improved Hb content within RBC, which enhances oxygen delivery to tissues. Gupta *et al*[16] reported a significant decrease in lactate dehydrogenase levels (LDH) from 527 U/L to 350 U/L (P=0.001) and serum bilirubin from 3.2 mg/dL to 1.5 mg/dL (P<0.001), indicating a reduction in haemolysis and improved overall red cell health.

Effect on ACS and stroke: Significant benefits were shown with HU therapy in reducing ACS, stroke, and other renal or hepatic complications associated with SCD. In a 24-month study by Jain *et al*[30], no recurrence of stroke or ACS were observed in children receiving HU (P<0.001). Similarly, Somkuwar *et al*[35] reported reduced incidence of ACS and stroke, while also demonstrating favourable renal and hepatic safety profile. Although transient renal (11.1%) and hepatic (8.3%) toxicity were noted, these effects were reversible, highlighting HU's long-term safety.

HU also led to shorter hospital stays; 5.16±1.29 days versus 6.55±1.7 days in controls (P<0.001) and reduced needs for analgesics, with HU-treated patients requiring a mean of 4.8 days for pain relief compared to 5.98 days in the control group[20].

Effect on pregnancy: HU showed potential benefits in managing SCD during pregnancy by reducing the frequency of VOC and improving overall maternal health outcomes. Although HU is typically withheld during pregnancy due to concerns about foetal safety, some studies indicate that, when carefully monitored, it can reduce acute painful episodes and decrease the need for blood transfusions, contributing to better maternal outcomes. Daigavane *et al*[32], reported that despite withholding HU in most pregnant women, it was reintroduced in severe cases to manage VOC, with improvements in clinical stability. Improved pregnancy outcomes with 73.8 per cent live birth rate[31] and no teratogenic effects[32] are also reported.

Long term efficacy of HU: Improved survival rates and better quality of life are reported with long-term and sustained use of HU in managing SCD. Voskaridou *et al*[37] observed that patients treated with HU for over 15 yr showed a significant reduction in mortality, fewer hospitalisations, and a marked improvement in overall health parameters. Similarly, the Multicentre Study of Hydroxyurea (MSH) highlighted that the continued use of HU over nine yr maintained increased levels of HbF, decreased rates of VOC, and significantly reduced the risk of complications like stroke and ACS[38].

HU safety: A total of 15 studies assessed safety related to HU treatment in SCD patients[10-12,14,15,21-23,27,30,32-36]. These studies evaluated adverse effects such as myelosuppression (*e.g*., neutropenia, thrombocytopenia), liver or renal toxicity, and other mild adverse events like skin pigmentation and rashes. Most reported that the side effects were mild and reversible, managed through dose adjustments or temporary discontinuation of HU. Favourable safety profile across multiple studies with most adverse effects being mild, reversible, and manageable are reported in multiple studies. The most commonly reported adverse effects included myelosuppression, such as neutropenia and thrombocytopenia. Neutropenia was observed in approximately 7-10 per cent of patients across the studies. Thrombocytopenia occurred in 6-8 per cent of patients, with most cases being mild and resolving with temporary discontinuation or dose adjustments. Studies have reported transient haematological toxicity with hydroxyurea, marked by a significant drop in WBC (3,000-4,000/mm^3; P<0.001) and ANC (2,000-3,000/mm^3; P<0.001). These changes were self-limiting and not associated with serious infections or clinical complications[16].

Haematological benefits of HU in managing SCD comprising decrease in WBC count from 13,560/mm^3 to 9,450/mm^3 (P=0.001)[12], and from 14,200/mm^3 to 8,600/mm^3 (P<0.001)[10], a reduction in ANC from 7,100/mm^3 to 4,200/mm^3 (P<0.001)[16], drop in platelet count from 430,000/mm^3 to 270,000/mm^3 (P=0.001)[27], a decrease in reticulocyte count from 14.5 per cent to 6.9 per cent (P<0.0001)[12] were observed after HU therapy.

Other mild adverse effects of HU, including skin pigmentation and rashes, occurred in 2-3 per cent of patients and did not necessitate intervention or discontinuation of HU therapy[23]. No significant long-term toxicities, such as hepatic or renal dysfunction, were reported. Only one study found higher rates of oligospermia (20%) and azoospermia (10%) in male SCD patients on HU compared to those not receiving it (18% and 4%, respectively), suggesting potential testicular dysfunction[34].

Discussion

Hydroxyurea has emerged as a cornerstone therapy for SCD demonstrating significant reductions in VOCs, blood transfusion needs, and hospitalisations. This systematic review affirms its well-established safety and good tolerability across diverse patient groups in India. Over the past 25 years, HU has shown substantial benefits in Indian settings, yet gaps in its optimal use and accessibility remain. Short-term benefits of HU are evident in Indian studies, but long-term data are lacking. International studies like the MSH with 17-yr follow up[39] and LaSHS (with a starting HU dose of 20 mg/kg/day gradually increased to 35 mg/kg/day)[37] show significant survival benefits, reduced painful episodes, ACS, hospitalisations and safety in paediatric populations over long periods. Additionally, HU has demonstrated safety in paediatric populations[37], with no significant long-term adverse effects on growth, development, fertility, or cancer risk over a 15-yr period. The absence of similar long-term follow-up in Indian studies limits assessment of HU's impact on chronic complications and fertility issues. This highlights the need for long-term studies in India to evaluate HU's efficacy and safety, especially concerning potential reproductive side effects, such as oligospermia and azoospermia in male patients.

Safety profile of HU in Indian studies aligns with global findings, showing mild, manageable side effects like neutropenia and thrombocytopenia. Regular CBC monitoring is crucial, especially where healthcare resources are limited. The transient nature of haematological toxicity underscores the need to educate healthcare providers and ensure patient follow-up on HU therapy.

Another important finding from this review is the variation in target populations and dosing strategies across studies. Despite NSCEM 2023 guidelines on dosing and target groups, many studies lack specification of treated age groups, affecting generalizability. The American Society of Haematology recommends starting HU in infants from nine months[40], while India often reserves it for symptomatic children older than two yr. This conservative approach may limit early intervention benefits, highlighting the need for more aggressive and standardised treatment protocols.

While HU's short-term efficacy in reducing VOC and transfusion requirements is clear, many Indian studies do not fully follow recommended monitoring protocols, such as regular CBC checks and dose adjustments. Transfusion practices vary widely across healthcare settings. This variability could influence the interpretation of transfusion-related outcomes included in this review. HU has also shown promise in managing thalassaemia by reducing transfusion dependency and improving Hb levels in patients with transfusion-dependent and non-transfusion dependent thalassaemia[41].

This review also identified key gaps in SCD management in India. While studies included diverse age groups and clinical manifestations, a targeted approach distinguishing tribal and non-tribal populations could provide valuable insights into the SCD burden and genetic modifiers affecting phenotypic variability. Further studies on pharmacokinetics, pharmacodynamics, and pharmacogenomics may refine HU dosing and enhance treatment outcomes.

A limitation of this systematic review is the heterogeneity of included studies, which varied in design, patient populations, HU dosing, and follow up duration. Formal risk of bias assessment was not performed, which may affect the robustness of conclusion; however, studies were selected based on predefined inclusion criteria.

India can establish comprehensive HU therapy guidelines incorporating flexible dosing strategies and treatment duration. Education, collaborations, and better healthcare access can enhance early detection, timely intervention, and community awareness of SCD. Increasing HU therapy adoption, affordability, and accessibility will benefit more SCD patients. With the availability of 200 mg capsules and 100 mg/mL suspensions, special attention to paediatric formulations and accurate weight-based dosing will further enhance treatment outcomes in these subgroups. Fostering patient education on HU adherence and establishing regular follow-ups can optimise outcomes and improve the quality of life for those living with SCD.

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