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Role of hydroxyurea therapy in the prevention of organ damage in sickle cell disease: a systematic review and meta-analysis

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Abstract

Background Hydroxyurea is an affordable drug that reduces vaso-occlusive crises and transfusion requirements in sickle cell disease. However, its effectiveness in preventing chronic organ damage is still unclear. This systematic review and meta-analysis aimed to evaluate the role of hydroxyurea in preventing organ morbidity.

Method We included original articles published in English from 1st January 1990 to 31st January 2023, reporting hydroxyurea therapy and organ damage from PubMed, Google Scholar, Scopus, and CrossRef databases. A total of 45 studies with 4681 sickle cell disease patients were evaluated for organ damage.

Results Our analysis showed that hydroxyurea intervention significantly lowered transcranial Doppler and tricuspid regurgitant velocity, with a standardized mean difference of − 1.03 (− 1.49; − 0.58); $I^2 = 96\%$ and − 1.37 (CI − 2.31, − 0.42); $I^2 = 94\%$, respectively. Moreover, the pooled estimate for albuminuria showed a beneficial effect post-hydroxyurea therapy by reducing the risk of albuminuria by 58% (risk ratio of 0.42 (0.28; 0.63); $I^2 = 28\%$).

Conclusion Our study found that a hydroxyurea dose above 20 mg/kg/day with a mean rise in HbF by 18.46% post-hydroxyurea therapy had a beneficial role in reducing transcranial doppler velocity, tricuspid regurgitant velocity, albuminuria, and splenic abnormality.

Systematic review registration PROSPERO CRD42023401187.

Keywords Sickle cell disease, Organ damage, Hydroxyurea, Meta-analysis

Introduction

Sickle cell disease (SCD) is a monogenetic disorder caused by a point mutation in the 6th position of the β-chain of globin, leading to abnormal hemoglobin production [1]. SCD is a major public health problem affecting more than 3,000,000 births globally. Predominantly found in Sub-Saharan Africa and India, the number of SCD cases is expected to increase by 30% in these regions by 2050 due to the high birth rate [2–4].

Studies have shown that Asian sickle cell patients have a relatively milder clinical presentation, compared to Africans. The presence of alpha-thalassemia, persistent high fetal hemoglobin (HbF) levels, genetic factors (BLC11A,

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HBS1L-MYB, and HBB loci), hematological parameters, social circumstances, climatic and geographical variation affect the clinical severity in SCD [5–10].

Under hypoxic conditions, Haemoglobin S (HBS) polymerizes and undergoes a rapid change in the shape of erythrocytes, leading to membrane destabilization, chronic hemolysis, systemic inflammation, and endothelial dysfunction. This leads to activation of adhesion molecules like P selectin, and platelet accumulation which give rise to small vessel obstruction and organ damage [11]. This is exacerbated by the ischemia/reperfusion process (I/R), macrovascular hyperemia, and microvascular hypoperfusion referred to as perfusion paradox. This condition is extremely challenging for vital organs like the brain, kidney, and heart, which may fail to respond and adapt to the need for increased oxygen [12]. Considering the unique combination and capability of different organs in handling hypoxia, innate immune response, coagulability, inflammatory and oxidative stress, and genetic, ethnic, and environmental age-dependent drivers, the spectrum of organ damage in SCD is diverse [13]. Chronic hemolytic anemia and recurrent episodes of ischemia–reperfusion injury contribute to progressive organ dysfunction.

Currently, hydroxyurea is the only ideal and affordable drug with global availability and good clinical efficacy for treating SCD patients. Hydroxyurea is a potent HbF inducer and myelosuppressor by nature [14, 15]. The National Heart, Lung, and Blood Institute (NHLBI) has recommended it to all sickle cell anemia children above 9 months of age irrespective of the clinical severity [16]. Hydroxyurea has excellent oral bioavailability and is rapidly cleared from circulation with a half-life of 2–3 h in both children and adults [17]. It is a well-tolerated drug with a few short and long-term toxicities with the most common toxicity being reversible cytopenia [15].

In a multicentric randomized controlled trial with 20 mg/kg/day hydroxyurea versus placebo (BABYHUG Trial) among SCD children aged 9–18 months, the authors found that children on hydroxyurea had lower rates of acute crises and hospitalization [18]. Dose escalation to a maximum tolerated dose of hydroxyurea has been shown to elicit significantly better hematological and clinical response compared to a standard dose of 20 mg/kg/day [19].

Despite enough evidence of hydroxyurea preventing acute symptoms in SCD, there is a lack of clarity on whether and to what extent hydroxyurea prevents organ damage in SCD patients. Therefore, this systematic review and meta-analysis are planned to investigate whether hydroxyurea therapy in SCD patients reduces organ damage and to evaluate the influence of HbF level and hydroxyurea dose in the prevention of organ damage.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched PubMed, Google Scholar, CrossRef, and Scopus for articles evaluating organ damage in SCD patients treated with Hydroxyurea. We used the following search terms: "Sickle cell Disease" AND "Hydroxyurea" AND "Organ Damage" (see Appendix 1 for the full search strategy). We included all the published articles from 1st January 1990 to 31st January 2023. Original articles in the English language with Abstract and/or Full text of articles for sickle cell disease patients screened for organ damage were considered. The studies included case reports, retrospective studies, letters to editors, cross-sectional studies, cohort studies, and randomized controlled trials. Articles either in a foreign language or not containing relevant information or review articles were excluded. Articles that evaluated the effect of hydroxyurea in SCD patients without the mention of organ damage were also excluded from the study.

Data analysis

Two reviewers AB and NK independently scrutinized and extracted the articles using Rayyan Software [20]. Conflicts and disagreements were resolved by discussion with the third reviewer, MM. The quality of the included studies was assessed using a modified Downs & Black checklist which scores each item as one point (yes) or zero (no), excluding the power question [21]. The total score determined the overall quality of the study, which was used to classify as good (25 and above), average (15–24), and poor (less than 15). Post-hoc power calculations were performed using G*power software and power scored using a 6-point scale [22].

The data was extracted by NK and AB using a standardized data format from studies that measured organ dysfunction/damage in SCD patients on hydroxyurea. Information was recorded in a customized electronic spreadsheet with details of authors, year of publication, study design, the study population country, type of publication, sample size, age, hydroxyurea dose, duration of hydroxyurea, HBF% at baseline, and follow-up and organ damage.

Data analysis was performed using the 'meta' and 'metafor' packages in R Studio, Build 576 with R for Windows. The software packages contain functions to estimate effect size with common effect and random effects, generate forest plots, and funnel plots, as well as sub-group and meta-regression analysis. The difference between the parameters for organ morbidity in SCD patients on hydroxyurea therapy and not on hydroxyurea therapy was calculated using a mean difference with a 95% confidence interval. The I^2 statistic was used to report the heterogeneity in the study,

whereas Funnel plots were used to report publication bias. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines were followed throughout this systematic review and meta-analysis [23]. The review protocol was registered in the International Prospective Register of Systematic Reviews, PROSPERO.(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=401187, registration number: CRD42023401187, accessed on 14 March 2023).

Results

We identified a total of 3267 articles with our search strategy. Of these, 1376 were removed as duplicates, and 1815 were excluded after screening titles and abstracts. Next, 76 articles were retrieved out of which 31 articles were excluded according to our exclusion criteria as mentioned. Finally, a total of 45 articles were included in the systematic review. The agreement between the reviewers was 82.5% (Cohen's kappa 0.97) and 100% before and after conflict resolution. The flowchart of the screening procedure is depicted in Fig. 1 and study characteristics are detailed in Appendix 2.

1) Central nervous system
a) Transcranial Doppler

Figure 2a shows the measurement of velocities of the cerebral artery by Transcranial Doppler (TCD)at baseline

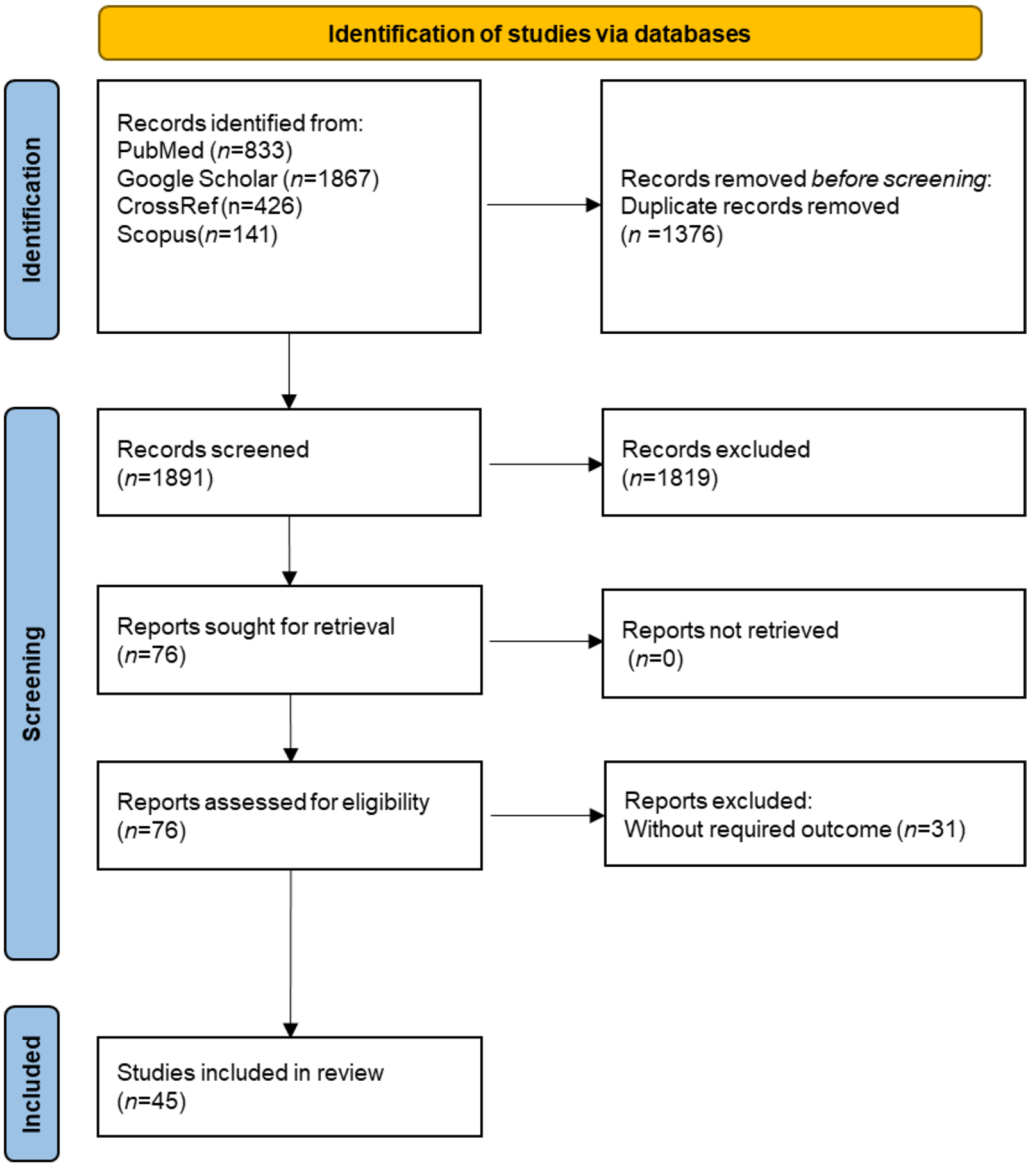
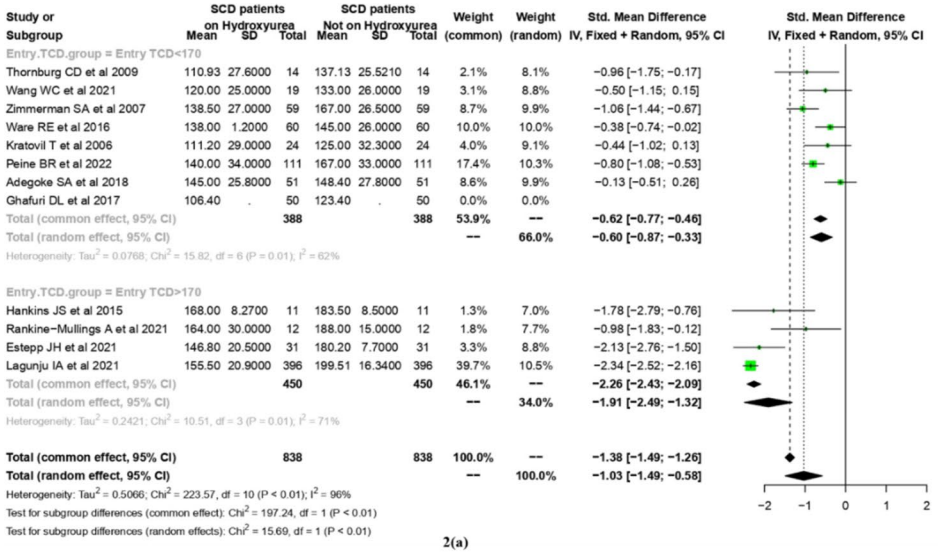
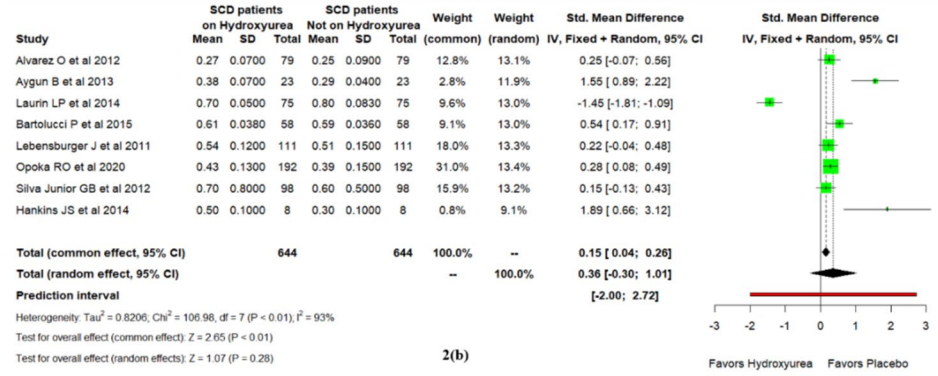


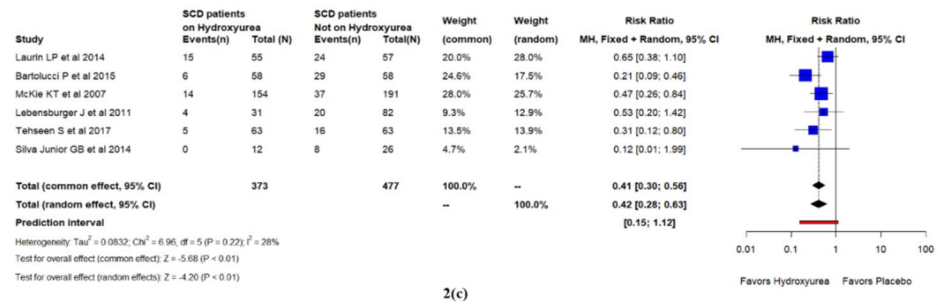
Fig. 1 PRISMA 2020 flowchart diagram for the study selection process



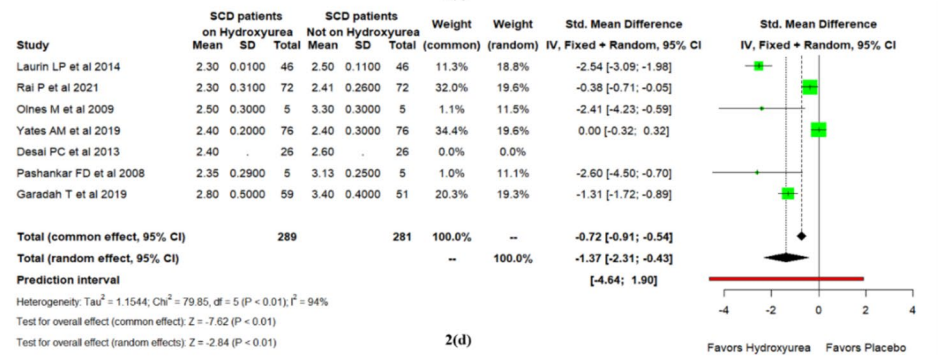
2(a)



2(b)



2(c)



2(d)

Fig. 2 Forest plot of **a** difference in transcranial Doppler flow velocities, **b** difference in creatinine levels, **c** risk ratio of microalbuminuria, **d** difference in tricuspid regurgitant velocities in sickle cell disease patients with or without hydroxyurea treatment

and post-hydroxyurea intervention of the included studies. The pooled estimates show a significant reduction in TCD velocity post-hydroxyurea treatment, with a standardized mean difference of − 1.03 (CI − 1.48, − 0.57; $p < 0{\cdot}0001$). The mean dose of hydroxyurea was 24·54 mg/kg/day, and the mean HbF level was 21.55% post-hydroxyurea therapy [24–35]. On meta-regression, we found that the covariates, including HbF % at baseline, dose, and duration of hydroxyurea therapy, and percentage increase in HbF post-hydroxyurea therapy significantly influenced the reduction of TCD Velocity, (see Appendix 4). Further subgroup analysis with baseline HbF% levels and duration of hydroxyurea therapy showed that baseline HbF% > 10 and hydroxyurea therapy irrespective of duration significantly reduced the TCD velocity (see Appendix 6). Among the studies with baseline TCD values above 170 cm/s, there was a significant reduction in TCD values after hydroxyurea therapy with a standardized mean difference of − 1.91(CI − 2.49; − 1.32; $p = 0.01$). In a study by Abdullahi SU et al. among 220 SCD children with a median age of 7.2 years having abnormal TCD (TAMMC ≥ 200 cm/s), the TCD value dropped to normal levels (< 170 cm/s) after a median duration of hydroxyurea therapy of 2.4 years. The TCD drop to normal levels was 48.9% (92) in the low-dose hydroxyurea arm(10 mg/kg/day) and 71.4% (95) in the moderate-dose hydroxyurea arm (20 mg/kg/day) [36].

b) Stroke

Table 1 shows the incidence rate of stroke in SCD patients. The incidence rate of stroke in SCD patients was slightly higher in those who were on hydroxyurea, but this difference was not statistically significant. The studies' mean dose of hydroxyurea and HbF levels post-hydroxyurea therapy ranged from 20 to 30 mg per kg per day and 14% to 23.1% respectively [27, 37–39].

c) Cerebral oxygenation

Hydroxyurea also improves cerebral oxygen saturation in SCD patients. In a study by Tavakkoli F et al. involving 31 SCD patients, which measured near-infrared spectroscopy (NIRS) to determine cerebral oxygen saturation, it was observed that cerebral oxygen saturation was significantly higher in SCD patients on hydroxyurea therapy than in those not on hydroxyurea therapy (46.1 ± 6.6 vs 41.2 ± 7.6, $p < 0.025$) [40]. Another study by Karkoska K et al. showed that cerebral oxygen saturation significantly increased after 2 years of hydroxyurea therapy in 55 SCD patients (65 to 72%, $p < 0.001$) [41]. A study by Kapustin D et al. among 27 SCD patients, showed that the mean white matter cerebrovascular reactivity was higher in hydroxyurea-treated patients compared to those who were not treated. (0.10 ± 0.03 vs 0.07 ± 0.03, $p = 0.08$) [42].

A study by Puffer E et al. among 65 SCD children, showed that SCD children on hydroxyurea therapy performed better on verbal comprehension, fluid reasoning, and general cognitive ability compared to SCD children not on medication [43]. A case report by Grace R F et al. showed that cerebral artery stenosis was normalized in a 4-year-old SCD child after 4 years of hydroxyurea therapy (17 mg/kg/day) [44].

2) Renal

a) Glomerular filtration rate

Table 2 shows the glomerular filtration rate (GFR) in SCD patients [24, 45–50]. The study by Alvarez O et al. reported an increase in GFR even after treatment with 20 mg/kg/day hydroxyurea, but this rise was significantly lower compared to age-matched SCD patients who were treated with a placebo [45]. In a study by Aygun B

Table 1 Incidence of stroke in SCD patients on hydroxyurea therapy and not on hydroxyurea therapy

Sr.no	Authors with year of publication	Mean age (months)	Not on hydroxyurea therapy			On hydroxyurea therapy			Hydroxyurea dose (mg/kg/day)
			N	Incidence of stroke /100-person year[a]	Mean HbF level	N	Incidence of stroke /100-person year	Mean HbF level	
1	Hankins JS et al. 2008	132	25	2.54	4	18	1.9	18.2	30
2	Wang WC et al. 2001	15	16	10	21.8	14	7.14	20.2	20
3	Nottage KA et al. 2016	113	50	4.04	5	30	1.1	14	20
4	Wang WC et al. 2021	149	19	3.82	8.2	9	11.10	23.1	23.8

Mean incidence rate of stroke in SCD not on hydroxyurea: 5.1, SD 3·3

Mean incidence rate of stoke on hydroxyurea: 5.31, SD 4.6

Unpaired *t*-test: $t = 0.0742$ df = 6 standard error of difference = 5.161

The two-tailed *P* value equals 0.9433

[a] Mean age of patients is considered as the total duration of non-exposure to hydroxyurea and the person-years is calculated by mean age in years X total number of patients

Table 2 GFR in SCD patients on hydroxyurea therapy and not on hydroxyurea therapy

Sr.no	Authors	*N*	Mean age (years)	GFR entry Mean (SD)	On hydroxyurea (months)	GFR exit Mean (SD)	Hydroxyurea dose (mg/kg/day)
1	Alvarez O et al. 2012	193	1.15	126.42 (38.8)[b]	24	146.64 (43·7)	20
2	Thornburg CD et al. 2009	14	2·91	139.2 (19.5)[b]	24	144.3 (15.69)	28
3	Aygun B et al. 2013	23	7.4	167 (46)[a]	25	145 (27)	24.4
4	Hankins JS et al. 2014	8	17.1	140.7 (17.5)	72	117.7 (22.5)	26.6
5	Silva Junior GB et al. 2014	26	32.1	105 (30)[a]	NA	112 (21)	1000 g[c]
6	Bartolucci P et al. 2015	58	35	124.5 (33.3)[a]	6	120.5 (2.83)	15 mg
7	Laurin LP et al. 2014	70	37	151 (55)[a]	73	128 (58)	1207 mg[c]

[a] Estimated GFR

[b] DTPA

[c] Dose of hydroxyurea per day

et al. in SCD patients with a mean age of 74 years, there was a mild reduction in GFR post-hydroxyurea therapy ($t=1.97$, df 44 standard error of difference = 11.122, $p=0.054$) [46]. The other 4 studies by Hankins JS et al., Silva Junior GB et al., Bartolucci P et al., and Laurin LP et al. were conducted in adult SCD patients in whom the GFR normally declines, making it difficult to conclude that hydroxyurea intervention reduced the GFR [47–50].

b) Serum creatinine

Figure 2b shows the measurement of serum creatinine in SCD patients [45–53]. The pooled estimates showed a slight increase in serum creatinine level after hydroxyurea intervention 0.36 (CI − 0.3, 1.01; $p=0.28$), but the difference was not statistically significant. The mean dose of hydroxyurea therapy was 21.20 mg/kg/day and the mean HbF level post-hydroxyurea therapy was 22.17%.

c) Urinary albumin

Figure 2c shows the measurement of urinary albumin levels in SCD patients [48–51, 54, 55]. The pooled estimates show a significant reduction in urinary excretion of albumin after hydroxyurea treatment with a risk ratio of 0.42 (0.28; 0.63); $I^2=28\%$; $p<0{\cdot}01$. The mean dose of hydroxyurea therapy in these studies was 19.17 mg/kg/day and the mean exit HbF level was 13.55%. On meta-regression, the covariates; hydroxyurea dose, and percentage increase in HbF after hydroxyurea therapy significantly influenced the reduction of albuminuria, whereas baseline HbF% and duration of hydroxyurea therapy did not affect the outcomes, (see Appendix 4). Further sub-group analysis was performed with baseline HbF% (< 10 or > 10) and age of SCD patients (< 18 years and > 18 years) in which we observed that baseline HbF levels did not influence the reduction of albuminuria. In contrast, adult patients had lower albuminuria compared to SCD children, (see Appendix 6).

d) Serum cystatin

In a study conducted by Alvarez o et al. among 193 SCD patients with a mean age of 13.8 months on 20 mg/kg/day hydroxyurea, the serum cystatin level at baseline and 24 months after hydroxyurea therapy were 0.91 ± 0.17 mg/l and 0.92 ± 0.13 mg/l respectively [44]. A similar finding was found in the study by Ayugun B in 23 SCD patients with a mean age of 7.4 years on a mean dose of 24.4 mg/kg/day hydroxyurea for 25 months, the serum cystatin level at baseline and post hydroxyurea therapy was 0.72 ± 0.09 mg/l and 0.74 ± 0.13 mg/l [46]. There was no significant difference in serum cystatin level after initiation of hydroxyurea therapy in SCD patients.

3) Spleen

SCD patients have splenic dysfunction which increases with age. Table 3 shows the splenic abnormality in SCD patients on hydroxyurea therapy and not on hydroxyurea therapy. Studies conducted by Hankins JS et al. and Santos A et al. showed that there was more than 90% of SCD patients aged above 10 years had markedly decreased or absent splenic function [37, 56]. In a study by Hankins JS et al. involving 43 SCD patients, 14% of SCD children had complete recovery of splenic function after the maximum tolerated dose(MTD) of hydroxyurea for a median period of 2.6 years [37]. Another study by Nottage KA et al. involving 40 SCD patients(mean age of 9.1 years) treated with a median dose of 27 mg/kg/day hydroxyurea for 3 years, showed that 33% of SCD patients had improved splenic uptake [57]. A similar finding was observed in

Table 3 Splenic abnormality in SCD patients on hydroxyurea therapy and not on hydroxyurea therapy

Sr.no	Authors with year of publication	Total number of SCD patients	Splenic uptake abnormality at baseline[ab]	Splenic uptake abnormality after hydroxyurea treatment	Hydroxyurea dose	Duration of hydroxyurea therapy (years)
1	Hankins JS et al. 2008 [36]	43	95%	81.40%	MTD up to 30–35 mg/kg/day	2.6
2	Hankins JS et al. 2005 [59]	14	NA	78.50%	30 mg ± 1.2 mg/kg/day	4
3	Nottage KA et al. 2014 [57]	40	77·50%	67.50%	20 mg escalated to MTD	3
4	Wang WC et al. 2001 [37]	17	100%	94.11%	20 mg/kg/day	2
5	Santos A et al. 2002 [56]	21	100%	92.85	15 mg/kg/day with dose escalation	1
6	Wang WC et al. 2011 [60]	144	38%	27%	20 mg/kg/day	2

Any gain in spleen function after hydroxyurea treatment is considered as normal splenic function

[a] At baseline or in the non-hydroxyurea group/placebo group

[b] Decline in splenic uptake from normal to decreased or absent, or from decreased to absent)

a study by Santos A. et al. where 6(42.85%) had mild to moderate improvement after hydroxyurea therapy with a maximum tolerated dose for 1 year [56]. Case reports of two SCD patients published by Susan Claster et al. in 1996, demonstrated that there was splenic regeneration in two adult SCD patients after hydroxyurea therapy [58].

In a study among 14 splenectomized SCD children (median age of 3.4 years) treated with hydroxyurea with a mean dose of 30 ± 1.2 mg/kg/day for 4 years, 43% of children had functional asplenia. There is a loss of splenic function in SCD patients even though they are on hydroxyurea therapy, but the loss was much lower compared to age-matched functional asplenia [58, 59]. In the BABY HUG Trial, for the pediatric SCD patients who were on 20 mg/kg/day, 19(27.14%) patients had decreased spleen function after 2 years compared to 28(37.8%) in the placebo group ($p=0{\cdot}21$) [60].

4) Cardiovascular

a) Tricuspid regurgitation velocity

Figure 2d shows the measurement of Tricuspid regurgitant velocities in SCD patients [50, 61–66]. The pooled estimates show a significant reduction in TRV post-hydroxyurea treatment with a standardized mean difference of $-1.37(\mathrm{CI}-2{\cdot}31,-0.42;\ p=0.004)$. The mean dose of hydroxyurea therapy in these studies was 22.66 mg/kg/day and the mean HbF level was 18.08%. Meta-regression of TRV showed that the covariates; HbF at baseline, and percentage increase in HbF after hydroxyurea therapy, significantly influenced the reduction of TRV velocity (see Appendix 4).

5) Avascular necrosis of hip joint

In a prospective study involving 40 SCD patients having a mean age of 12.9 ± 4.2 years at enrolment, 11(27.5%) had avascular necrosis (AVN) hip joints of varying severity. Post hydroxyurea therapy of 20 mg/kg/day, 2(6.9%) developed new AVN. Five (50%) of SCD patients who were on hydroxyurea for more than 5 years had the worst AVN hip joint [66, 67]. In another prospective study by Kris M. Mahadeo et al. among 257 SCD patients screened for osteonecrosis of the femoral head, the prevalence of avascular necrosis of the hip joint who were on hydroxyurea therapy was 18(21.68%) which was higher compared to the prevalence of AVN who were not on hydroxyurea therapy 8(8.08%) [68].

6) Retina

A study by Estepp JH et al., among 123 SCD children aged ≤ 19 years, revealed that 10.6% developed retinopathy. In SCD children who never developed retinopathy, hydroxyurea was initiated at a median age of 8.8 years with a median MTD of 26 mg/kg/day whereas, in SCD children who developed retinopathy, hydroxyurea was started at 10.6 years with a median MTD of 27 mg/kg/day. Children treated with hydroxyurea who never developed retinopathy had higher HbF levels (20.8%) at the last clinical follow-up compared to HbF levels (12.5%) at the time of diagnosis in children who developed retinopathy [69].

7) Respiratory system

SCD patients develop progressive changes in pulmonary function testing with decreased lung volumes and flows. The airflow limitation and airway hyperresponsiveness are associated with increased morbidity and

premature death. In a study conducted among 56 SCD patients, hydroxyurea therapy for a mean period of 4.7 years showed significantly improved rates of decline in FEV1 and FEF25-75% and FVC [70]. In another study by Kotwal N et al., 62 SCD children (mean age 9.8 ± 3.8 years) were treated with hydroxyurea, and 30 SCD children (mean age 10.7 ± 4.9 years) were not on hydroxyurea. The authors observed a significant increase in forced vital capacity in the hydroxyurea group after 3 years of follow-up while children in the non-hydroxyurea group showed a decline in forced vital capacity after 2.6 years of follow-up (7.2 ± 17.1 vs 3.4 ± 18.2, $p < 0.01$) [71]. Hydroxyurea therapy in children with SCA leads to improvement in annual pulmonary function decline.

Meta-regression on the factors affecting the effect of hydroxyurea in preventing organ damage. The meta-regression results predict the protective role of hydroxyurea therapy on TCD velocity, albuminuria, and TRV of SCD patients (Appendix 4). In the case of TCD velocity, HbF baseline ($p = 0.007$), therapy duration ($p < 0.001$), percent increase in HbF ($p < 0.001$) as well as HU dose ($p = 0.018$) significantly affected the TCD velocities. However, in the case of albuminuria, only the HU dose ($p < 0.001$) and percent increase in HbF ($p < 0.001$) affected the albuminuria levels. Similarly, only the HbF levels at baseline ($p < 0.001$) and the percent increase in HbF ($p < 0.002$) affected the TRV levels in SCD patients.

Discussion

This is the first systematic review to investigate the effects of hydroxyurea treatment on multi-organ dysfunction in individuals with SCD. Our review included 45 studies with a total sample size of 4681. Randomized controlled trials, cross-sectional studies, cohort studies, case–control studies, and case series were included in our meta-analysis. Of the 45 studies included, 11 were classified as poor (score less than 15), 28 were classified as average (score between 15 and 24) and 6 were classified as good (score of 25 and above). Effects of hydroxyurea were assessed before and after treatment in terms of different indicators of organ function.

For assessing brain infarction/stroke risk, TCD velocity in the cerebral artery above 200 cm/s is indicated as an increased risk of stroke in SCD patients. The pooled estimates of 12 studies that reported the TCD velocities before and after hydroxyurea therapy showed a significant decrease in TCD velocity in SCD patients. The results were influenced by the dose and duration of hydroxyurea therapy, baseline HbF%, and percentage rise in HbF levels. The mean dose of hydroxyurea ranged from 20 mg/kg/day to 27.9 mg/kg/day (mean 23.14 mg/kg/day) and the post-hydroxyurea therapy HbF levels ranged from 11.79% to 25.9% (mean 18.46%). Further subgroup analysis suggested that SCD patients who had higher baseline HbF levels had a more significant reduction in TCD velocity. Four studies measured the incidence of stroke in SCD patients before and after hydroxyurea therapy and the overall incidence of stroke was slightly higher in SCD patients on hydroxyurea therapy compared with those not on hydroxyurea therapies. The limitations to comparing the incidence of stroke in two groups were (a) mean age was considered as the total duration of non-exposure of hydroxyurea for calculating the incidence of stroke in person-years, (b) age is an important risk factor for stroke, as age increases, there is always a greater risk of stroke and there can be an increased incidence of stroke after treatment of the hydroxyurea group, (c) there is wide variability in clinical severity in SCD patients and there are SCD patients who are susceptible to stroke.

GFR, serum creatinine, and microalbuminuria are the parameters used to assess renal dysfunction. GFR in SCD increases from infancy till early adulthood and thereby declines to normal levels [68]. Studies in SCD patients below the mean age of 3 years showed a slight increase in GFR, but it was significantly lower compared to those who were not treated with hydroxyurea. This suggests that hydroxyurea intervention in younger patients potentially prevents a rise in GFR. However, the measurement of GFR as a marker for renal dysfunction in older SCD patients is not accurate, as the GFR normally declines after the second decade of life [72]. The meta-analysis of six studies reporting microalbuminuria levels before and after hydroxyurea therapy showed that hydroxyurea therapy significantly reduced the microalbuminuria (risk ratio 0.42 (0.28; 0.63); $I^2 = 28\%$; $p < 0.01$). Furthermore, subgroup analysis showed that hydroxyurea therapy irrespective of baseline HbF level has a protective role against renal dysfunction. This protective role was more significant in adults compared to children. Pooled estimates from eight studies measuring serum creatinine before and after hydroxyurea therapy found a slight increase in mean creatinine levels after therapy with a standardized mean difference of 0.36(CI − 0.3, 1.01; $p = 0.28$). This can be explained by the fact that creatinine is a relatively late marker of renal damage and hydroxyurea therapy may or may not be beneficial once there is significant kidney dysfunction.

Sickle cell disease (SCD) can cause various cardiovascular complications such as pulmonary hypertension, left ventricular diastolic heart disease, myocardial infarction, and dysrhythmia. The pooled estimates of the 6 studies showed that the TRV was significantly reduced post-hydroxyurea therapy with a mean dose of 22.66 mg/kg/day and the mean HbF level post-hydroxyurea therapy was 18.08% suggesting that hydroxyurea therapy was

beneficial in preventing cardiac dysfunction in SCD patients. TRV reduction was influenced by baseline and percentage rise in HbF. Concerning respiratory complications, there were only two studies that reported a beneficial effect of hydroxyurea in preventing the decline of pulmonary function test parameters.

Studies conducted by Hankins JS et al. 2008 Hankins JS et al. 2005 Nottage KA et al. 2014, Wang WC et al. 2001, Santos A et al. 2002, and Wang WC et al. 2011 showed a reduction in splenic uptake abnormality post-hydroxyurea therapy. In the BABY HUG Trial, the splenic abnormality was lower in the hydroxyurea group compared to the placebo group, but this difference was not statistically significant. Case reports also have shown splenic regeneration after hydroxyurea therapy. Overall, from the studies, we can conclude that hydroxyurea therapy helps in preserving splenic function to some extent, even though the results might not be statistically significant in RCT when compared to placebo.

There is limited evidence to suggest whether hydroxyurea therapy has any role in preventing liver dysfunction and retinopathy in SCD patients. In addition, there is limited evidence regarding the avascular necrosis of the hip joints in patients who are on hydroxyurea therapy. It has been postulated that hydroxyurea therapy increases fetal hemoglobin and hematocrit leading to increased blood viscosity and sickling in the microcirculation of the femoral head [68].

It is now evident that hydroxyurea in a dose of above 20 mg/kg/day (mean 23.14 mg/kg/day) with a rise in HbF% post hydroxyurea therapy of (mean 18.46%) prevents major organ dysfunction in the brain, kidney, heart, and spleen. All these RCTs are done on SCD patients in Africa or on those of African origin. Arab Indian haplotypes have higher baseline HbF levels and overall clinical severity in these patients is less even though some of them despite high HbF may have a severe phenotype. Suboptimal dose of hydroxyurea is a serious concern in the treatment of SCD patients and there is a need to evaluate the efficacy of suboptimal dose of hydroxyurea therapy in the prevention of organ complications, especially in patients with high baseline HbF.

Meta-regression analysis of multiple factors influencing the effectiveness of hydroxyurea therapy in preventing organ damage showed that few factors such as baseline levels of HbF, duration of hydroxyurea therapy, dose of hydroxyurea as well as percent increase in HbF levels post therapy significantly affected the outcome. However, these effects could only be studied in the TRV, TCD, and albuminuria outcomes. The other outcomes could not be analyzed due to a limited number of studies.

Our study has several limitations. Firstly, the included studies were diverse and differed in mean age, dose, and duration of hydroxyurea therapy. Secondly, the parameters studied for various organ dysfunction were not uniform and the duration and dose of hydroxyurea varied in each study. Thirdly, most of the studies were observational with very few randomized controlled trials conducted only on the African SCD population. Very few studies were available that evaluated avascular necrosis of the hip joint in SCD patients.

Conclusion

Hydroxyurea has been proven through randomized controlled trials to be an effective drug in reducing acute sickle-related events in patients with sickle cell disease. Our meta-analysis has shown that hydroxyurea can reduce TCD velocity, TRV, and urinary albuminuria, potentially reducing organ damage. However, the role of hydroxyurea in preventing stroke is inconclusive and needs more evidence. In addition, the beneficial effect of hydroxyurea in dysfunction of the liver, retina, pulmonary system, and avascular necrosis of the hip joint needs to be further evaluated. Therefore we conclude that hydroxyurea therapy may be effective in preventing organ damage in Sickle cell disease patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02461-z.

Additional file 1: Appendix 1. Search terms and search strategy. **Appendix 2.** Study characteristics of the included studies. **Appendix 3.** Mean hydroxyurea dose and exit HbF levels. **Appendix 4.** Meta-regression. **Appendix 5.** Funnel plots and sensitivity analysis. **Appendix 6.** Subgroup analysis. **Appendix 7.** Full-length studies excluded with reasons for exclusion. **Appendix 8.** Data quality of included studies. **Appendix 9.** PRISMA 2020 checklist.

Authors' contributions

NK: conceptualization, data curation, methodology, project administration, supervision, writing—original draft, writing—review and editing. AB: conceptualization, data curation, methodology, project administration, supervision, writing—original draft, writing—review and editing. SA: data curation, formal analysis, resources, software, visualization, writing—review and editing. NSK: data curation, formal analysis, resources, writing—review and editing. NM: data curation, formal analysis, resources, writing—review and editing. MM: conceptualization, project administration, supervision, writing—review and editing. All authors reviewed, edited, and approved the final manuscript.

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Availability of data and materials

All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
Not required.

Competing interests
The authors declare that they have no conflict of interest.

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