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Effects of Hydroxyurea or Chronic Blood Transfusion on Renal Function in Children with Sickle Cell Disease

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Abstract

Renal complications are common in children with sickle cell anemia (HbSS). No treatment is proven to slow progression of sickle cell nephropathy (SCN). Both hydroxyurea (HU) and chronic blood transfusion (BT) reduce common complications of sickle cell disease; little has been reported regarding the effect of these treatments on renal function.

We did an extensive assessment of renal function (estimated glomerular filtration rate (eGFR), renal osmolality, renal protein, fractional excretion of sodium (FeNa), trans-tubular potassium gradient (TTKG), and phosphorus re-absorption) on children (age 7 years-21 years) receiving these treatments for other sickle cell complications. Nine patients on BT (duration 26.7±10.7 mo) and 17 on HU (56.1±45.9 mo) with HbSS were enrolled. There was a high prevalence of hyper-filtration (mean eGFR of 150.2±31.7 ml/min/1.72 m^2 and 172.0±31.7 ml/min/1.72 m^2 in HU and BT groups, respectively), with a trend (p-0.06) toward less hyper-filtration in the HU group. Overall, 18.75% and 20.8% of patients from both groups have microalbuminuria and proteinuria respectively. Our data confirm a high prevalence of sickle cell nephropathy despite these disease modifying treatments. Further larger, longitudinal studies, importantly including untreated controls if possible, are necessary to clarify the impact, if any, of HU or BT on sickle cell nephropathy

Keywords: Sickle cell nephropathy; hyper-filtration; Proteinuria; Microalbuminuria

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Introduction

Sickle cell disease (SCD), including HbSS, is one of the most common hematologic hereditary disorders, affecting 1 of every 396 black newborns in the U.S [1]. Though adults with HBSS have a median survival only into the fifth decade [2], the number of individuals with SCD in the U.S. may approach 100,000 [3].

More than a century ago, sickle-shaped red blood cells (RBCs) were described by James Herrick in a West Indian student presenting with fever, leg ulcers, and respiratory symptoms [4]. The misshaped RBCs were ultimately found to be due to a single mutation in the beta globin gene [5] which favors polymerization of deoxy-hemoglobin; polymers elongate the cell, compromise blood flow and create a "vascular logjam" leading to vaso-occlusion [6]. In addition, inflammation, oxidative stress, endothelial activation, and release of vasoactive substances including prostaglandins and nitric oxide contribute to the clinical pathology, leading to multiple organ involvement, including kidney injury [7].

Kidney involvement was first noticed by Dr. Joseph Hugh, who reported "a tendency to fixation of specific gravity of the urine" in 1928 [8]. Since then, many additional renal complications have been discovered, including impaired urinary acidification, cortical scarring, hyper-filtration, hematuria, proteinuria and renal failure. This constellation of defects is known as sickle cell nephropathy (SCN) [6,9–11]. End-stage renal disease (ESRD) develops in 4–18% of patients with HbSS necessitating dialysis and/or kidney transplantation [12]. The mean survival after developing ESRD is 4 years; 40% of patients will die within 20 months of starting dialysis [13].

Despite this significant morbidity and mortality, no specific treatment of SCN has been established. ACE inhibitors have been demonstrated to reduce proteinuria [14], but long-term impact on SCN progression is unknown. Blood transfusion attenuates the frequency of acute pain and chest episodes [15,16] and has been shown to rescue the kidney from loss of concentrating ability if given very early in life, prior to age of 10 years [17,18]; however, and long term effect on the kidney, if any

has not been reported Hydroxyurea was licensed by the FDA in 1997 for use in adults with moderate to severe sickle cell disease (based on frequency of acute pain and chest syndrome) and has shown to be similarly effective in children and recently young infants [19-21]. It is an antineoplastic drug that inhibits ribonucleotide reductase, increases fetal hemoglobin concentration in red blood cells, and has other potentially beneficial effects, including improved nitric oxide availability, reduced red cell -- endothelial interaction, and decreased erythrocyte density [16,22]. HU is efficacious not only in decreasing painful events and acute chest syndrome but also reduces need for transfusions and improves survival in HbSS [16,23]. There are little data regarding the effect of HU on renal function. Studies report possible beneficial effects on proteinuria and microalbuminuria, and stabilization of GFR after 2 years of HU treatment [24,25]. A randomized trial of HU in young children with HbSS (BABY HUG) found glomerular hyper-filtration, present at baseline, worsened over two years of observation, regardless as to whether or not HU was given [19,20]. There was some improvement in concentrating ability in the group who received hydroxyurea.

Our study was designed to look comprehensively at renal function in children receiving chronic transfusion therapy or hydroxyurea to determine whether we might detect any impact on renal involvement.

Materials and Methods

Patient population

A cross-sectional observational study of effects of HU or chronic BT on the prevalence of sickle-cell nephropathy was undertaken at SUNY Downstate Medical Center from June 2012 to August 2013. The Institutional Review Board of SUNY Downstate Medical Center approved the study. Written informed consent was obtained from patients, or the guardians of participants under age 18; written assent was also obtained from patient's age 7 years to 17 years.

During the study period, approximately, 90 active pediatric patients with HbSS were approached. Patients aged 7 years to 21 years with HbSS who were on HU or chronic BT for at least 3 months prior to the beginning of the study or who were not on treatment (controls) were eligible for enrollment. Patients were enrolled at the time of a routine outpatient clinic visit or scheduled blood transfusion at the outpatient transfusion suite. Blood and urine samples were collected at the next routine visit (to ensure first morning urine collection after a recommended but unobserved fast).

Samples were collected when patients were in their normal state of health, free of painful crisis or inter current illnesses. Laboratory studies were performed as listed below on the same day as the first morning urine collection. Blood was obtained just prior to transfusion in the transfused group.

Laboratory studies

The following parameters were tested: RBC, Hb, HbF, reticulocyte count, MCV, WBC, urine osmolality, serum chemistry, fractional excretion of sodium (FeNa), fractional re-absorption of phosphorus, transtubular potassium gradient (TTKG), urinary protein-to-creatinine ratio and urinary microalbumin-to-creatinine ratio. The estimated glomerular filtration rate (eGFR) was calculated using the updated pediatric bedside Schwartz formula: eGFR = 0.413 x (height in cm)/(serum creatinine in mg/dL) [26].

Serum and urine creatinine were measured using a modified kinetic Jaffe procedure and urine protein was measured using a colorimetric method. Both measurements were done on Olympus AU analyzers. Serum and urine osmolality were measured utilizing advanced micro-osmometer model 3MO. All laboratory procedures were done in SUNY Downstate Medical Center's clinical laboratory.

Data regarding dose and duration of treatment with HU and frequency and duration of chronic blood transfusions were collected from the patients' charts.

Student's t-test was used to compare parameters between the groups.

Results

Patient characteristics

Originally 51 African-American patients with HbSS age 7 years to 21 years signed consent to participate in the study: Seventeen and 28 were receiving chronic BT or HU, respectively, and 6 patients were enrolled as controls. Patients were receiving chronic BT for primary (abnormal transcranial Doppler ultrasonography [27]) or and secondary stroke prevention prior to study enrollment. Transfusion was scheduled to maintain the concentration of Hb S less than 30 percent of the total in most patients, though some were allowed a nadir of 50 percent after several years of more aggressive transfusion [28]. Red cells were given by simple transfusion, sometimes preceded by phlebotomy of 5 mL/kg–10 mL/kg of patient blood, depending on total hemoglobin concentration and percent sickle hemoglobin. Nearly all patients were receiving chelation therapy with deferasirox, 20 mg/kg/day–40 mg/kg/day.

Children were receiving HU for a variety of clinical indications, similar to those described at St Jude in 2010 [29]. An initial dose of 20 mg/kg/day was escalated to a target neutrophil count of 2.0 – 4.0 $\times 10^9$/L, as described [30]. Complete blood counts were monitored monthly, and Hb F and liver and renal function screen were performed at least every three months.

Due to non-adherence to clinic visits and sample collection difficulties, recruitment of a control group was abandoned and data from 8 and 11 patients from the chronic BT and HU groups, respectively, were discarded as incomplete, leaving a total of 26 patients for analysis, 9 and 17 in the chronic BT and HU groups, respectively.

The 26 patients (50% female) ranged in age from 7 years to 21 years at the time of enrollment and had been treated with chronic BT or HU for at least 3 months, range from 14 to 156 and from 9 months to 60 months, respectively. Patient characteristics are presented in Table 1.

There was no statistically significant difference between groups with regard to age, sex, or BMI. There was a statistically significant difference in treatment duration and blood pressure values between the two groups.

Hematological and renal data are presented in Table 2. As expected, HbF percentage and MCV were significantly higher in the HU patients than in the patients receiving chronic transfusion; reticulocyte counts were also higher in the HU group. There were no significant differences between the two groups in the renal parameters examined, although there was a trend (p=0.06) toward higher eGFR in the transfused patients; both groups exhibited hyper-filtration.

Overall, 18.75% and 20.8% of patients from both groups have microalbuminuria and proteinuria respectively.

Table 1: Characteristics of 26 patient's ages from 7 years to 21 years with HbSS SCD.

	HU group	Chronic BT group	P value
Patients (n) Males (n) Females (n)	17 10 7	9 3 6	
Age (years)	10.8±3.8	13.5±9.1	0.21
BMI (kg/m^2) Percentile for age Z-score	17.2±2.3 41.8±33.3 -0.22±1.03	17.0±4.4 30.8±32.0 -0.40±1.26	0.44 0.21 0.34
Systolic BP (mmHg) Percentile for age and height Z-score	102.4±9.6 41.8±27.0 -0.28±0.86	110.7±11.1 70.3±27.7 0.74±0.96	0.02 0.009 0.005
Diastolic BP (mmHg) Percentile for age and height Z-score	56.7±6.7 36.5±21.4 -0.46±0.73	63.2±7.4 57.2±18.8 0.17±0.52	0.01 0.01 0.01
Treatment duration (months)	26.7±10.7	56.1±45.9	0.03
Treatment dose (mg/kg/day)	24.7±1.9	n/a	n/a

Table 2: Laboratory results in the 2 groups of patients with HbSS.

	HU group	Chronic BT group	P value
HbF (%)	13.5±5.8	4.5±3.9	0.0005
Retic (%)	9.6±4.0	8.4±0.02	0.02
MCV (fL)	103.5±14.5	91.8±7.2	0.02
Urine osmolality (mOsm/kg)	433.9±110.7	479.6±92.3	0.15
Fractional excretion of sodium (FeNa) (%)	0.32±0.2	0.38±0.3	0.25
Reabsorption of phosphorus (%)	95.3±2.9	95.7±1.5	0.34
Transtubular potassium gradient (TTKG) (%)	4.05±2.9	3.10±1.6	0.27
Microalbumin/creatinine (mg/mg)	70.3±125.1	83.3±101.5	0.43
Protein/creatinine (mg/mg)	0.2±0.4	0.19±0.1	0.47
eGFR (ml/min/1.73m^2)	150.2±31.7	172.0±37.7	0.06

Discussion

Patients with SCD have a variety of renal structural and functional abnormalities that progress with age. The occurrence of kidney failure is described in 4% to 18% of adult patients with SCD and is associated with increased mortality [12,31,32]. The primary goal of this study was to evaluate whether clinical use of HU or chronic BT might impact on the prevalence of SCN as compared to children not receiving anti-sickling therapy. Unfortunately, families not receiving monthly treatment by either of these modalities found specimen collection unwieldy or impossible and we were not able to collect data on controls. We understand that the lack of a control group makes evaluation and comparison of the results in both treatment groups more difficult and less valuable. HU and chronic transfusion groups had similar renal function, not substantially different from that expected in adolescents with Hb SS.

We found that children receiving HU had higher fetal hemoglobin and MCV, than chronic BT patients, as that documented in previous studies of the effect of HU on patients with SCD [20,33]; somewhat surprisingly, reticulocyte counts were also higher in the HU group.

Published data for the effect of HU on renal function describe a variable effect on reducing proteinuria and microalbuminuria [24,24]. Some studies show a protective effect of higher hemoglobin level itself on the level of proteinuria and microalbuminuria [34]. Microalbuminuria is rare before the age of 7 years, but the frequency of microalbuminuria in the population of 10-18 year olds is 20-40%. Overt proteinuria is reported at the level of 20 to 56% in adult population [31,35-38]. In our study we did not find a significant difference in the level of proteinuria and microalbuminuria between two treatment groups. The overall prevalence of proteinuria and microalbuminuria in both groups was similar to that reported in untreated children with Hb SS.

We did not find a difference in renal tubular function between the two groups, as assessed by measurement of fractional sodium excretion (FeNa), potassium excretion (transtubular potassium gradient (TTKG)), fractional re-absorption of phosphorus, and urine osmolality. Published data on tubular dysfunction in patients with HbSS show significant distal tubular abnormalities such as diminished potassium excretion and low urine osmolality. However, hyperkalemia has not been reported to occur in sickle cell patients unless there is significant renal functional impairment [39,40]. Sodium re-absorption is usually normal or slightly increased and phosphorus re-absorption is increased [41,42]. Our results showed normal FeNa, high normal phosphorus re-absorption, and normal potassium excretion in the absence of hyperkalemia, without any difference between HU and chronic BT groups. Our findings possibly can be explained by the young age of our patients and, as a consequence, shorter disease duration. Alternatively, therapeutic intervention may have reversed tubular dysfunction, as we originally speculated; unfortunately our planned controls are lacking.

Patients with HbSS clinically demonstrate an inability to concentrate urine. In young children it has been observed that maximal urine osmolality can be increased by multiple blood transfusions. However, the capacity to improve renal concentrating ability is progressively lost with age and, eventually, the defect becomes irreversible. A maximum urine osmolality of 400 mOsm/kg–500 mOsm/kg of water is typically seen in adults with HbSS under water deprivation [43-45]. Results from the BABY HUG study suggest that 24 month HU treatment significantly preserved urine concentration ability in young children [33,46], although fluid deprivation was suboptimal.

We found a renal concentrating defect in both HU and chronic transfusion groups, with respective average urine osmolalities of 433±110.7 mOsm/kg *vs* 479±92.3 mOsm/kg of water (p=0.15) after at least 6 hours of fasting. The lack of effect of HU on renal concentrating capacity in our study possibly can be explained by late initiation of HU treatment (average duration of HU treatment was 26.7±10.7 months and average patient age was 10.8±3.8 years). Chronic transfusion therapy was similarly started relatively late in childhood, at about the same age.

Our data show a high prevalence of hyper-filtration with a mean eGFR of 150.2±31.7 ml/min/1.72 m^2 and 172.0±31.7 ml/min/1.72 m^2 in HU and chronic BT groups, respectively. This difference is not statistically significant (p=0.06) but there is a tendency for a lower level of hyper-filtration in children with HbSS treated with HU. Overall, the finding of hyper-filtration is correlated with many previous studies in adults and children that showed a prevalence of hyper-filtration in 30.5 to 51% of patients. The tendency toward a lower level of hyper-filtration possibly attributable to treatment with HU was previously reported in some studies and not found in others, perhaps explained by patient age differences among the studies [19,20,24,25,33,47]. Most studies estimating GFR, including our own, use a creatinine-based assessment. This is known to be suspect in individuals with sickle cell disease due to abnormal tubular excretion of creatinine [48].

Of note, we found significantly lower systolic and diastolic blood pressure in the HU group. This finding may be worth further assessment in future investigations. However, our chronic transfusion patients were nearly all being transfused due to either stoke or risk of stroke; blood pressures may be relatively elevated in such individuals [49]. Also, it is worth investigating further whether higher BP, although in an acceptable range, is a contributing factor to the tendency of higher hyper-filtration rate in the chronic transfusion group.

Our study has several limitations. A large number of subjects, especially those not on chronic therapy and recruited as controls, were unable to complete the expected evaluations, leaving us without a control study group. Renal abnormalities were prevalent in both our groups, but it is unknown whether either (or both) treatments may have impacted. All of the BT patients were receiving deferasirox, which can be nephrotoxic [50]. Patients in the BT group were on treatment longer than patients in HU group, though age at initiation of treatment was similar. A possible explanation for the high prevalence of renal dysfunction in both groups may have been the relatively advanced age at initiation of either treatment. The use of an HU dose (24.7±1.9 mg/kg/24 hrs) lower than the maximum tolerated dose (30 mg/kg/24 hrs–35 mg/kg/24 hrs) may be suboptimal [51]. Finally, our use of the Jaffe reaction to measure serum and urine creatinine may have overestimated the level of creatinine compared to the enzymatic method [52].To conclude, we have thoroughly assessed renal function in a large group of children with sickle cell disease receiving several years of commonly used disease attenuating therapies. Our data confirm a high prevalence of sickle cell nephropathy despite these treatments. We fully accept several significant limitations of the study, such as the lack of a control group, a wide variation in the treatment duration in both groups, and the lack of consideration of the possible confounding effects of nephrotoxic medications, such as deferasirox, on the outcome. Further larger studies, importantly including untreated controls if possible and, ideally, longitudinal, are necessary to clarify the impact of HU or chronic blood transfusion on sickle cell nephropathy.

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