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Original Research Article

Low dose oral hydroxyurea prophylaxis improves all clinico: haematological parameters among sickle cell disease patients

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ABSTRACT

Background: Sickle cell disease (SCD) an inheritable disorder of haemoglobin structure resulting from substitution of valine for glutamic acid at 6th position of β-globin chain of haemoglobin(HbS), which polymerizes on deoxygenation and undergoes to sickle shaped RBC causing vaso-occlusive painful crisis, chronic haemolysis, anaemia, frequent blood transfusions, frequent hospitalizations with increased morbidity and acute chest syndrome leading to mortalities. Presence of foetal haemoglobin (HbF) prevent sickling and use of drugs like Hydroxyurea (HU) results in increased production of HbF to prevent complications of SCD. Aims and objectives was to know the various effect of low dose HU on clinical and haematological parameters among SCD patients.
Methods: Total 100 S HbSS patients were consecutively selected, with indication for HU in 10mg/kg + 5mg folic acid/day. Baseline haemoglobin, HbF, HbS, haematocrit (HCT), TRBC, MCV, MCH, MCHC, and HbS, TPC, TWBCs, ANCs and other relevant tests as needed. Follow up haematological tests were done at 1 month and then every 3 month up to 24 months with monitoring of clinical status, hepatic, renal, and myelotoxicities. Data were collected and analyzed.
Results: There were 31 paediatric cases with mean age of 8.47±4.1 years and 69 adults with mean age of 25.9±8.2 years presented with or history of various complications. HU improves all clinical and haematological parameters significantly (Hb, HCT, HbF, MCV, MCH, MCHC,) with mild myelotoxicities (decreased ANC, TPC, WBCs).
Conclusions: HU improves all clinical and haematological parameters with mild myelotoxicities among SCD patients.

Keywords: Clinical, Hydroxyurea, Haematological, Parameters, Sickle cell disease

INTRODUCTION

Sickle cell disease (SCD) is a heritable haemoglobinopathy (autosomal reccecive) resulting in abnormal haemoglobin called Sickle Haemoglobin (HbS).[1-3] It is a disorder of structure of haemoglobin, where glutamic acid is replaced by valine at 6th position of β-globin chain resulting in HbS. Individuals are said to be sickle cell disease (SCD), when they have one of several genotypes that results in at least ≥50% of haemoglobin being HbS.

The abnormal HbS polymerizes under hypoxic conditions and undergoes sickling resulting in occlusion of microcirculation and the hall mark sings of clinical sequel are vaso-occlusive painful crisis (VOC), chronic haemolysis, frequent infections, haemolytic jaundice, gall stones, splenic infarction, avascular necrosis of bones, growth retardation, organ damage and premature death due to acute chest syndrome.[4] The normal life span of RBCs (120 days) is reduced to 15-30 days.[5,6] It causes significant morbidity , mortality and poor quality of life and economic burden to the patients and his/her families.

Painful crisis (VOC) is the most common reason for emergency hospitalization and acute chest syndrome is the most common cause of deaths.

Foetal haemoglobin HbF (α2γ2) has higher oxygen affinity and interferes with HbS polymerization, but its levels start to decline soon after birth and are negligibly present in adults. The presence of HbF in significant amount in SCD patients altered the course of the disease.[7] This leads to effort to raise the HbF level in SCD patients by using drugs like hydroxyurea (HU), azacitidine etc.

The traditional therapy of sickle cell crisis includes use of hydration, analgesics and blood transfusions. Cure of the disease with allogenic bone transplantation is still elusive to common people. HU is an anti-neoplastic agent, is the only approval disease modifying therapy for SCD in adults (USFDA 1999).[8] It is a S-phase specific ribonucleotide reductase inhibitor that acts on bone marrow and by its cytotoxic effect enhances maturation of erythroid precursors there by increases the HbF formation.

Recently it has been suggested that, Nitric oxide (NO) produced by hem group oxidation of HU can activate soluble guanylate cyclase, increasing gamma globin gene expression and consequently HbF synthesis. Other possible pleotrophic effects are decrease in adhesion of neutrophils and reticulocytes to vascular endothelium, however, there are several unanswered questions pertaining to its doses, duration of therapy and potential long-term safety and toxicity.[9,10]

Several studies have reported beneficial effects of HU therapy in lower doses of 20-25mg/kg/day with no attempt to achieve the maximum tolerated dose (MTD), i.e. 30-35mg/kg/day.[11,12] However, sickle cell patients responds variably to HU therapy. The potential of HU to be mutagenic in-vivo and even carcinogenic effect had not been fully evaluated.[13] Recent studies have been reported that, significant DNA damage in leukocytes of SCD patients with HU at a dose of 20-30mg/kg/day.[14] The possible deleterious effects of HU in human spermatogenesis have been recently reported.[15,16]

SCD is prevalent in western part of Odisha state of India with a high prevalence of 21-40% of population. The reports on effect of HU on haematological parameters in sickle cell disease is scarce. Keeping with high cost and potential myelotoxicity of HU in mind, this study was undertaken to know the effect of HU on clinico-haematological parameters in SCD patients with a fixed low dose HU of 10mg/kg/day.

METHODS

It was a prospective, open label, observational study conducted between October 2011 to October 2013 at VSSIMSAR, Burla after approval of Institutional ethics committee. Selection criteria were HbSS patients with history of frequent VOC (>3 episodes/year), anaemia with frequent blood transfusion (>2 units/year), jaundice, acute chest syndrome (≥1 episodes last year), nephropathy, avascular necrosis of bone, transient ischemic attacks (TIA), strokes, priapism, and adherence to HU therapy for ≥80% of dose and the duration of study period. Exclusion criteria was patients with sickle β-Thal, HbSC, HbS-SD Punjab, pregnancy, iron and vitamin B_{12} deficiency state, severe hepatic and renal impairment and non-adherence to HU of <80%. Total 100 cases of sickle cell patients were consecutive recruited for the study.

Baseline investigations were done i.e. complete blood counts i.e. DC, TLC, Hb%, TRBC, Hematocrit (HCT), MCV, MCH, MCHC, HPLC (High Performance Lipid Chromatography) of haemoglobin, Total platelet counts (TPC), ANC (Absolute Neutrophil Counts). Other relevant tests done were liver function tests (LFT), USG (Ultrosonography), blood urea nitrogen (BUN), X-ray chest, and hip and shoulder joints. Dose of HU was fixed to 10mg/kg/day + Folic acid 5mg to all cases by oral route after written consent of patients or his/her care taker/relatives.

Follow up was done at 1 month and then every 3month for 24 months with monitoring of renal toxicity (serum creatinine levels >50% above baseline), hepato-toxicity (LFT more than 2 fold from baseline), myelotoxicities (Absolute neutrophil count<2500/m³, TPC <80,000/m³, Hb <4.5gm% or 20% ↓ in Hb% from initial). If toxicity of any one occurs then withdrawal of HU for 2-3 weeks till the recovery and restarted again with regular follow up was done. Data were collected, and statistics were done using paired T test and Chi-square test using GraPad InStat Version 3.00 for Window and data was considered statistically significant at P value <0.05.

Aim of the study was to know the changes in various clinical and haematological parameters in pediatrics and adults SCD patients, with a fixed low dose of HU of 10mg/kg/day.

RESULTS

Total 100 patients, out of which 31 were paediatrics (Age <14 years) and 20 were male and 10 female and 69 were adults (Age >14 years) of which 49 were male and 20 were female. Mean age of paediatrics patients was 8.47±4.1 (2-14 yrs) and for adults it was 25.9±8.2 (15-46 yrs). Majorities (34%) were between 11-31 yrs and 31% were between 21-30 yrs and presented with different clinical features singly or in combination (Table 1).

Changes in VOC

The baseline mean VOC in paediatric patients was 3.93±3.2/year and at 24 months it was 0.8±0.7 and there was decrease of 79.6% (p=0.0001). In adult baseline mean VOC was 3.9±1.5 and decreased to 1.4±0.6 and there was decreased of 64.1% (p=0.0001).

Table 1: Clinical features present in both paediatrics and adults groups before hu therapy.

In paediatrics cases			In adults cases		
Clinical features	**No. of paediatric cases**	**%**	**No. of adult cases**	**%**	**Statistics**
Anaemia	26	83.9	59	85.5	X^2 =0.044, P =0.8322
Jaundice	23	74.2	45	65.2	X^2 =0.4332, P=0.5104
Splenomegally	23	74.2	41	59.4	X ^{2}=1.476, P=0.2308
Cholelithiasis	5	18.1	21	30.4	X^2=1.592, P=0.2070
AVN	2	6.5	19	27.5	X^2=4.537, P=0.0333
CKD	3	9.7	3	4.4	X^2=0.3395, P=0.5601
VOC	22	71.0	60	86.9	X^2=2.71, P=0.1009
BT (blood transfusion)	13	41.9	18	26.1	X^2=4.000, P=0.0455
ACS (Acute Chest Syndrome)	0		2	2.9	X^2=0.0343, P=0.8530

Table 2: Changes Hb in Gm% Fractions by HPLC of haemoglobin before and after HU Therapy.

In Paediatrics					In Adults			
Hb fractions	**Pre-HU**	**Post-HU**	**P value**	**% Changes**	**Pre-HU**	**Post-HU**	**P value**	**% Changes**
HbF%	22.6±5.33	25.7±4.9	0.0001	13.7	19.3±6.0	23.9±6.0	0.0001	23.8
HbS%	72.8±5.2	69.24±4.7	0.0001	-4.9	75.06±5.85	70.86±5.17	0.0001	-5.6
HbA_O %	2.02±0.7	2.18±0.7	0.3068	7.9	2.36±0.7	2.22±0.7	0.1616	-5.9
HbA_2 %	2.52±0.7	2.6±0.6	0.6754	3.2	2.5±0.9	2.9±0.8	0.0038	16

Table 3: Increased in Mean Hb in gm% after HU therapy in different times.

SCD patients	Pre HU Hb Gm%	3 M	6 M	9 M	12M	15 M	18 M	21 M	24 M
Pediatrics	8.15	9.37	9.80	9.62	9.48	9.47	9.59	10	10.21
Adults	8.35	9.59	10.32	10.25	10.68	10.39	10.68	10.86	11.04

Table 4: Decrease in TWBC (10^3/µl) after HU therapy at different time.

	Pre HU	3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M
Paediatrics	8.8	8.7	7.8	8.6	8.3	8.36	8.16	7.44	7.33
Adults	10.8	9.9	9.7	9.23	9.37	9.26	9.4	9.01	9.65

Changes in blood transfusion (BT)

Requirement of baseline BT in paediatrics was 2.16±1.93/yr and decrease to 0.32±0.54/yr and it was decreased to 85.2% (p=0.0001) and in adults baseline BT was 1.14±1.2/yr and it was decreased to 0.16±0.32, there by decrease of 85.9% (P=0.0001).

Changes in hospitalization rates

Rates of hospitalization at baseline was 0.90±1.62/yr in paediatric and decreased to 0.35±0.48 (61%), (p=0.0001). In adults it was 1.52±1.2 and decreased to 0.25±0.5 (83%), (P=0.0001).

Changes in HbS fractions by HPLC OF haemoglobin before and after HU therapy

The HbS fraction at baseline was 72.8±5.2% and decreased to 69.24±4.7% (-4.9%), (P=0.0001) in paediatrics and in adults it was 75.06±5.85% and decreased to 70.86±5.17% (-5.6%), (p=0.0001). Thus, there was 4.9% and 5.6% decrease in mean HbS at 12 months of HU in pediatrics and adults respectively. (P=0.0001) (Table 2).

Changes in HbA_2 levels before and after HU therapy

The HbA_2 was 2.52±0.7% and increased to 2.6±0.6) (+3.2%), (p=0.6254) in pediatrics and it was 2.5±0.9% and increased to 2.9±0.8% (+16%) and (P=0.0098) (Table 2).

Changes in haemoglobin (Hb) in gm% at different times from baseline after HU therapy in both groups

The baseline mean Hb% was 8.14±1.83 and 8.35±1.6gm% in paediatrics and adults respectively and it was increased to 10.2±1.93(25%) after 24 months of HU in pediatrics and to 11.0±1.8gm% (31.7%) in adults. The

increased in Hb % was significant at 3rd months of initiation of HU therapy (Table 3).

Changes in foetal haemoglobin (HbF) levels before and after HU therapy in both groups

Baseline mean HbF was 22.9±5.9% in male and 21.9±4.03 % in female paediatrics patients. In adults it was 19.3±6.6 % in male and 18.5±4.2% in female. There was no sex wise significant difference in baseline HbF%. Baseline HbF was increased from 22.6±5.33 to 25.7±4.9 (13.7%, p=0.0001) in paediatrics and in adults it increased from 19.3±6.0 to 23.9±6.1 (23.8%), and (P=0.0001) (Table 2).

Changes in haematocrit (HCT) levels before and after HU therapy

The baseline HCT in paediatrics was 24.4±5.44 and 26.2±6.3 in adults. The HCT increased to 24.1% and 26.34% in paediatrics and adults respectively.

Changes in TRBC levels before and after HU therapy

The baseline TRBC was 3.03 and 3.15±0.67/µl in paediatrics and adults respectively and increased to 3.15±0.67 and 3.65±0.71/µl in paediatrics and adults respectively (p=0.05).

Changes in MCV before and after HU therapy

The baseline MCV was 89.01±10.2 and 83.2±11.4 fl in paediatrics and adults respectively and it was increased to 94.9±7.6 fl (15.7%) and to 92.6±10.5 fl (11.3%) in paediatrics (p <0.005) and adults (p < 0.05) respectively after 24 months of HU.

Changes in MCH before and after HU therapy

The baseline MCH was 27.3±2.8 and 27.0±3.9pq in paediatrics and adults respectively and it was increased to 32.03±2.4 (+10%) and to 30.7±4.7 (+13.7%) in paediatrics and adults respectively after 24 months of HU therapy. (p <0.005).

Changes in MCHC before and after HU therapy

The baseline MCHC was 32.7±4.5, 32.6±3.7gm/dl in paediatrics and adults respectively and increased to 33.8±1.6 (+3.56%) and to 33.1±2.1gm/dl (+1.53%) in paediatrics and adults respectively at 24months of HU therapy.

Changes in TWBC levels before and after HU therapy

The baseline TWBC was 8.8±3.05 and 10.8±4.2 $x10^3$ /µl in paediatrics and adults respectively and it was decreased at 24 months to 7.3±2.2 (-17%) and decreased to 9.7±3.8$x10^3$/µl (-10.2%) in adults. There was significant lower TWBC at 6th months in paediatrics and at 9th months onwards in adults (Table 4).

Changes in absolute neutrophils counts (ANC) before and after HU therapy.

The baseline absolute neutrophil count (ANC) was 4470.9±1608.1 and 6379.9±3066.1/µl in paediatrics and adults respectively and was decreased at 24 months of HU therapy in paediatrics to 3987.5±1185.4 (-10.83%) and decreased to 5509.7±2507.9/µl (-13.64%) in adults. The decrease in mean ANC was significant in 9th months onwards to 21 months (p<0.05). In 28 patients (11 paediatrics and 17 adults) developed decreased ANC of <2500/µl.

Changes in total platelet counts (TPC) before and after HU therapy

The baseline total platelet count (TPC) was 258.3±152.7 and 299.5±174.2/µl in paediatrics and adults respectively and it was decreased at 24 months in paediatrics to 206.4±127.0/µl (-20.1%) and decreased to 261.4±148.3/µl (-12.7%) in adults. The decrease in TPC was significant at 12 and 15 months of therapy in adults (p<0.05) and in rest of follow up. In 8 patients (3 paediatrics and 5 adults) develop transient thrombocytopenia of <80,000/µl, but not manifested clinically.

Changes in serum bilirubin levels before and after HU therapy

Baseline mean serum bilirubin level was 2.57±1.6 and 2.71±1.9mg/dl in paediatrics and adults respectively and decreased to 1.8±0.7 (-30%) and to 1.56±1.11mg/dl (-42.4%) in paediatrics and adults respectively. The decreased in mean bilirubin at 24 months was significant in both groups (p <0.0002).

DISCUSSION

In our study of 100 patients, there were 31 paediatrics cases, out of which 21 were male and 10 were female and in adults of 69 cases 49 (71%) were male and 20 (29%) were female. The mean age in paediatrics group was 8.47±4.2 and in adults it was 25±8.2 years. Anaemia was commonest finding in both groups (paediatrics 26 (83.6%) and adults 59 (85.5%). Jaundice was present in 23 (74.2%) of paediatrics and 45 (65.2%) of adults. Splenomegally was present in 23 (74.1%) of paediatrics and 41 (59.2%) of adults. Hepatomegally was present in 11 (35.4%) of paediatrics and 28 (40.6%) of adults and cholelithiasis was present in 5 (16.1%) of paediatrics and 21 (30.4%) of adults. Avascular necrosis was present in 2 (6.5%) of paediatrics and 19 (27.5%) of adults and nephropathy in 3 (2.6%) of paediatrics and 3 (4.34%) of adults.

The clinical response to HU was statistically significant in all parameters in both groups of patients in our study. The decrease in frequency of VOC, BT and hospitalization was 79.6%, 85.18%and 61.15 respectively

in paediatrics and 64.1%, 85.9% and 83.5% in adults respectively. Charache et al, reported decrease in VOC more significantly in their MSH study of 50%, 58% decrease in BT and 30% decrease in hospitalization.[17-19] These values were similar to Portuguese hospital study by Braga et al, showed 80% decrease in VOC, 69% decrease in hospitalization and 67% decrease in BT.[20] Robert PF et al reported 30% less hospitalization than other study.[21] In this study requirement of BT was decreased to 85.1% and 85.96% in paediatrics and adults was comparable of 95% decrease reported by Patel DK et al, in the same population indicating that 10mg/kg/day HU may be a good option than the MTD in SCD patients.[22] The mean HbF% in our study was 22±5.3 and 19.3±6.0 % was similar to Patel DK et al observed in 2012.

Singh H et al, observed mean baseline HbF of 12.83% and increased to 13.7% in paediatrics and 23.8% in adults after 1 year of HU therapy.[23] In Belgian study by Foster A et al, reported only 5% increase, was lower than Portuguese hospital study of 25% and 49% by Braga et al, and Singh H et al.[12,20,23] In our study, 3 paediatrics and 7 adults there was no increase in HbF levels rather decreased. In MSH study 50% cases had no increase in HbF after 24 months of study and genetic variance, bone marrow exhaustion and variability in drug bioavailability has been explained.[20,21] Regano P et al, reported increase in mean total Hb, HbF and decrease HbS, WBC, platelet counts and LDH levels. Acute chest syndrome was reduced to 29.3% (p 0.001), VOC of (-34.1%, p 0.001), hospitalization rates by (-53.2%, p 0.001) and bone necrosis by (-6.9%, p 0.001). New silent cerebral infarctions in increased by (+42.4%, p 0.001) but not stroke (+0.5%, p 0.572).[24]

In our study HbS was decreased significantly by 4.9% and 5.6% in paediatrics and adults respectively and increased HbF levels leading to decreased frequency of VOC. At 24 months of HU therapy there was increase in mean Hb level of 25.3% and 31.7% in paediatrics and adults respectively in our study which was higher than reported by Patel et al, of 16.7% and Singh H et al of 9%. MCV increased by 15.7% and 11.3% in paediatrics and adults in our study which was higher than reported by Patel DK et al, of 5.8% and Singh H et al of 8%. In our study MCH increased by 10% and 13.7% in paediatrics and adults was comparable to 11.8% and 7.6% reported by Patel DK et al.

In this study TLC, ANC and platelet count decreased, but the trend was not uniform and values were statistically not significant. Transient myelotoxicity in 11 (35%) paediatric and 17 (24.6%) adults had ANC of < 2500/µl, which was significantly higher than 0% reported by Patel DK et al. In our study 2 (9.7%) of paediatrics and 5 (7.24%) of adults had decreased in TPC to <80,000/mm^3 which was similar to 7.5% decrease reported by Patel DK et al. However, these myelotoxicity were not associated with any clinical manifestations and the parameters improve with short-term withdrawal HU of 2-3 weeks.

In our study, serum total bilirubin decreased by 30% and 42.4% in pediatrics and adults respectively at 2 years of follow up due to decrease haemolysis, which was comparable to 25% and 49% reported by Patel DK et al.[22] There was no reports of hepatic, nephrotoxicity, drug rash, hyper pigmentation and any evidences of malignancy during the study period. However, the questions of possibility of risk of leukomogenesis, effect on growth and fertility can be answered by long-term follow up. Compliance in HU therapy is more important to achieve sustained increase in Hb gm% and clinical effects in SCD patients. In children it may prevent chronic organ damage which will be enormous impact on morbidity and mortality. Despite having higher levels of HbF (22.6%) in paediatrics and 19.3% in adults some patients have severe course of disease. Myelotoxicities was found in 36 patients (8 paediatrics and 28 adults), which is transient and reversible with temporary withdrawal.

CONCLUSION

Hydroxyurea prophylaxis improves all clinical and haematological parameters of sickle cell disease by increasing production of HbF and prevent sickling , vaso-occlusive painful crisis and end-organ damages and by decreasing haemolysis prevent anaemia, jaundice and need for blood transfusions , rates of hospitalization and other complications in both paediatrics and adults SCD patients. However, risk of myelotoxicities, fertility and growth retardation in children needs long term study to answer.

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