ORIGINAL RESEARCH

Hematological effects of hydroxyurea inchildren with sickle cell disease

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ABSTRACT

Background and Aim: It is well known that hydroxyurea impacts hematologic indices in sickle cell disease (SCD), we aimed to evaluate the effect of hydroxyureahematological improvement in children with sickle cell anemia in our Indian based setup.**Methods and Materials:** Its an ambiperspective observational study which was conducted at our tertiary care center for a duration of 1 year and 8 months. After recording complete history190 patients were enrolled and started on Hydroxyurea and followed up every 2 months till 1 year, at every follow up, total Hb, HbF levels, MCV, MCH were compared before and after treatment with Hydroxyurea for one year. **Results:** Of 190 total recruited patients, 84 were studied at the end because of loss to follow-up due to various reasons. Significant increase in haemoglobin, RBC indices(MCV and MCH) and HbF were noted (p<0.05).**Conclusion:** The use of hydroxyurea in our native population increasestotal Hb, HbF levels, MCV andMCH before and after treatment with Hydroxyurea for one year in sickle cell patients.

Key words:SCA, Hydroxyurea,total haemoglobin, HBFlevels, MCV,MCH

INTRODUCTION

Sickle cell anemia is a autosomal recessive disease in which there is mutation of B globin gene resulting in substitution of guanine with valine at 6th position in the B globin chain of haemoglobin resulting in haemoglobinopathy, characterised by formation of Hemoglobin S, This variant which polymerizes abnormally rendering red blood corpuscles easily deformable, sticky, and shape like a sickle,these abnormal RBC attachesto the endothelium of small venules thus promote unpredictable episodes of microvascularvaso-occlusion and premature RBC destruction resulting in haemolytic anemia. Major clinical features include episodes of ischemic pain and ischemic or frank infarction within the spleen, CNS, bones, liver, kidneys and lungs[1]. In India, SCD is a common hemoglobinopathy, next to thalassemia. The prevalence of carrier state of sickle cell varies from 1% to 40% among different tribal groups. Madhya Pradesh has maximum load with an estimated number of 67,861 sickle homozygote and 9, 61,492 sickle heterozygote. Out of 45 districts in Madhya Pradesh, 27 districts fall into sickle cell belt. The prevalence of sickle cell varies from 10% to 33% in Madhya Pradesh. It has also been estimated that 13,432 pregnancies would be at risk of getting a toddler with SCD in Madhya Pradesh and thus the expected annual births of sickle homozygote would be 3358 [2]. Although the SCD is present from birth, but symptoms are rarely seen before age of 3-6 months with an increased incidence of adverse events coincident with the physiologic fall in fetal Hb (HbF)[3]. SCA was first described in south Indian tribal groups and subsequently in central India[4]. Only cure for SCD is bone marrow transplantation, which usually necessitates a human lymphocyte antigen-identical family member donor. Hurdles in widespread use of bone marrow transplantation in patients with SCD include a scarcity of suitable bone marrow donors and therefore the got to identify patients with an adequate risk-to-benefit ratio[5]. Due to these reasons, drug therapy for SCD continues to be the first and primary mode of disease management that focus specially in decreasing the complications of this disease[6]. Hydroxyurea was first tested in SCD in 1984 since then Till date hydroxyurea, which is a

myelosuppressive agent, is that only effective drug proven to decrease frequency of painful episodes. It acts by increasing the level ofHbF in blood, which opposes the polymerisation of HBs thus prevention episode of hemolysis resulting in rise in total Hemoglobin level. It was developed as an anticancer drug and is also been used to treat myeloproliferative disorders-leukemia, melanoma and ovarian cancer. Side effects; includes anorexia, nausea, vomiting, low absolute neutrophil count (ANC), bone marrow suppression, elevation of liver enzymes and infertility[7]. Recent evidence documents sustained long-term benefits with prevention or reversal of chronic organ damage[8].Although questions remain regarding its long-term risks and benefits, current study is conducted to analyzehematological response in patients of SCD receiving Hydroxyurea.

Aim and objectives were to study Total haemoglobin, HbF levels, MCV, and MCH,before and after starting hydroxyurea therapy in children of SCA.

Present study was carried out at MGM medical college Indore from January 2019 to August 2020. After review of synopsis of research, approval by ethical committee and talking written informed consent from parents patients with SCD were included in study population.

SOURCE OF DATA

All patients attending dept. of paediatrics, M. Y. hospital, Indore and Chacha Nehru BalChikitsalayaEvamAnusandhan Kendra, Indore. The study sample was based on the prevalence of SCD, in Madhya Pradesh. Minimal sample size was required in the study is 84 by using the formula sample size is n=4pq/L^2 Where P is prevalence of the disease under study, q=1-p; L is the tolerable error in the estimation of the prevalence (5%). Prevalance of SCD in general population in Madhya Pradesh is 30%.

STUDY DESIGN

It was retrospective and prospective (ambispective) observational study.

INCLUSION CRITERIA

Diagnosed cases of SCD by Hb electrophoresis were included in the study.

EXCLUSION CRITERIA

Patients <2 years of age, HIV reactive patients and patients already on hydroxyurea therapy before enrolment were excluded.

A detailed history, clinical examination, and specific baseline investigations (Complete blood count [CBC], liver function test [LFT], renal function test [RFT], HIV, Hb electrophoresis), were done before starting Hydroxyurea therapy detailed history questionnaire and Medical records used.The typical starting dose of hydroxyurea was 15-20 mg/kg/day and doses were adjusted according to ANC (target to be to maintained between 2000 and 2500). Then patients were called for follow-up every 2 months till 1 year. On follow-up total haemoglobin, RBC indices (MCV and MCH) and HbF was noted. On follow-up specific investigations including CBC, RFT, and LFT done. On each follow up if any, side effects were investigated.

If neutropenia <1500/ul and thrombocytopenia<80,000 occurs, hydroxyurea therapy was with hold and monitor CBC with white blood count differentially. When blood counts recover, reinstitute hydroxyurea therapy. Data analyzed as pre-treatment and post-treatment of hydroxyurea therapy.

STATISTICAL ANALYSIS

The data were collected from the proforma of the study and then was compiled in the Microsoft excel software for the master chart. Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data. Chi-square test, Wilcoxon Signed rank test, Friedman test, and unpaired t-test was used to calculated p value.

RESULTS

During study 190 sickle cell patients recruited for study.

Total recruited patients=190, lost to follow-up=106, study population at 12 months=84 (out of which 57 were SCA and 27 SCD). Out of 84 patients, 34-male and 46 female.

Table 1 shows that the majority of sickle cell patient in our study belong to 6-10 year of age.

Table 1: Age distribution of study population

Age	No of Patients	Percent
1-5 year	10	11.9
6-10 year	42	50
11-15 year	24	28.6
>15 year	8	9.5
Total	84	100.0

After use of Hydroxyurea total Hemoglobin increased significantly fron mean of 7.639 to 8.808 (p<0.05) (Table 2)

Table 2: Total Hemoglobin before and after hydroxyurea therapy

	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
Total HB before hydroxyurea	84	7.639	1.1031	5.0	10.3	Lower 7.4 Upper7.8	<0.01
Total HB after Hydroxyurea	84	8.808	0.8617	7.0	11.0	Lower 8.621 Upper8.995	

After use of Hydroxyurea MCV increased significantlyfron mean of 77.19 to 83.14 (p<0.05)(table 3)

Table 3: MCV before and after hydroxyurea therapy

	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
MCV before hydroxyurea	84	77.19	8.93	61	96.6	Lower 75.252 Upper79.127	<0.01
MCVafter Hydroxyurea	84	83.14	10.64	68	107	Lower 80.830 Upper85.447	

After use of Hydroxyurea MCHCincreased significantlyfron mean of 32.65 to 34.73 (p<0.05)(table 4)

Table 4: MCV before and after hydroxyurea therapy

	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
MCHC before hydroxyurea	84	32.65	1.36	30.0	35.7	Lower 32.351 Upper32.942	<0.01
MCHCafter Hydroxyurea	84	34.73	1.50	32.0	38.4	Lower 34.403 Upper35.054	

After use of Hydroxyurea HBFincreased significantlyfron mean of 22.86 to 28.44 (p<0.05)(table 5)

Table 5: Fetal Hemoglobin before and after hydroxyurea therapy

	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
HBF before hydroxyurea	84	22.86	7.44	8.30	49.40	Lower 21.247 Upper24.474	<0.01
HBFafter Hydroxyurea	84	28.44	7.47	6.80	42.90	Lower 26.820 Upper30.061	

DISCUSSION

Hydroxyurea is a standard and accepted therapy for SCD but is less frequently used in our region and also there are no studies regarding its efficacy and side effects in our native SCD population. So, in our study, we used Hydroxyurea as a treatment modality for SCA in order to evaluate its efficacy and safety. A study by Ndefo*et al*., also suggests that although bone marrow transplantation can cure SCD, it is an impractical solution for most third world countries, which have a high disease burden.Even in the U.S., bone marrow transplantation is limited by the availability of donors. Pharmacological therapies are effective at reducing complications of SCD and are safe and easily administered and they continue to prolong the life expectancy of patients[6].

In our study it was observed that therapy with Hydroxyurea for 12 month duration leads to significant rise in the mean value of Haemoglobin. (From 7.6±1.1031 g/dl to 8.8±8.808 g/dl with P value<0.0001)in Study by SomasundaramJayabose[9]. There Was Significant Increase In Mean Value Of Haemoglobin (7.2 gm/dl To 8.5 g/dl P Value 0.001)after 12 Month of Hydroxyurea Therapy. This increase in mean value of haemoglobin may be due to decrease in haemolysis with Hydroxyurea therapy due to rise in HbF level and decrease in Hbs level thus helps in maintaining mean haemoglobin value.

In our study it was observed that therapy with Hydroxyurea leads to significant rise in the mean value of MCV (mean corpuscles value) (from 77.19±8.93flto 83.14±10.64 fl,p value 0.001).In a study by Patel *et al*., also there was significant rise in MCV with Hydroxyurea therapy (MCV (fL) raised from 80.7 +/-8.7 to 85.4 +- 8.8 p value<0.0001)[9].In a study by Ana Cristina Silva-PintoI,after hydroxyurea therapy for 12month. The MCV increased from 88.7 ± 13.5 to 104.8 ± 15 fl (P value 0.001)[10].This reason for increase in MCV in our study may be due to increase in HbF and decrease in Hbs due to which mean corpuscle volume increases.

In Our Study It Was Observed That With Hydroxyurea Therapy the Mean Value Of MCHC Was Raised From 32.65±1.36g/dl To 34.73±1.50 g/dl And It Was Significant With P Value <0.0001In a study by Patel eta al also with Hydroxyurea therapy for 12 month there was significant rise in the value of MCHC (32.0g/dl to 34.1g/dl with p value 0.0100)[15].This rise in MCHC may be due to increase in size of RBC which may be loaded with more quantity of Haemoglobin thus MCHC increases.

In our study it was also observed that with

hydroxyurea therapy for 12month there was significant rise in mean value of HbF from 22.86± 7.44g/dl to 28.44± 6.80 g/dl with p value <0.001. In a study by Sunil K. Pondugala*et al*.,inhydroxyurea group, mean fetal hemoglobin percentage after 12 months was 39.77 ± 8.92 as opposed to entry mean fetal hemoglobin percentage of 28.38 ± 8.85 reflecting a statistically significant increase in mean fetal hemoglobin percentage (p<0.001). Whereas in placebo group, mean fetal hemoglobin percentage after 12 months was 24.91 ± 5.28 as opposed to entry mean fetal hemoglobin percentage of 24.52 ± 4.81 (P = 0.297) showing a statistically significant increase in mean fetal hemoglobin percentage after 12 months of hydroxyurea therapy[11].In a study by deshpande*et al*., it was observed that after 12 month of hydroxyurea therapy there was significant rise in HbF from 14.54 to 24.70 with p value <0.001[12].This rise in Fetal hemoglobin with hydroxyurea may be due to induction through soluble guanylylcyclase activation and altered erythroid kinetics.

LIMITATIONS

As the patients come to our setup from distant places, loss to follow up was a major setback because of distance as well as economic constraints for travelling.

CONCLUSION

In our study, we enrolled 121 patients out of which only 84 were able to complete the scheduled follow-up at regular interval of 2 months, i.e., 2, 4, 6, 8, 10, and 12 month. We recorded the baseline value of total haemoglobin, MCV,MCHC and fetal haemoglobin(HBF).We followed the patients at regular interval of 2 months and the above mentioned parameter was compared with the baseline parameter. It was found thathaematological parameter areaffected positively like rise in Total Hb, MCV,MCHC and HbF. So after evaluating the above data, we could conclude that Hydroxyurea is an effective inincreasing in Total Hb, MCV,MCHC and HbF. Thus this improve in haematological parameter impoves overall clinical status of the patients. Thus based on the above study, we can recommend regular use of hydroxyurea in our native population at our setup in Indore.

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REFERENCES

1. Bhatia HM and Rao VR. Genetic Atlas of the Indian Tribes. New Delhi: Institute of Immunohematology, Indian Council of Medical Research; 1986.
2. Colah RB, Mukherjee MB, Martin S and Ghosh K. Sickle cell disease in tribal populations in India. Indian J Med Res. 2015;141(5):509-515.https://doi.org/10.4103/0971-5916.159492.
3. Negi RS. Sickle cell trait in India. A review of known distribution. Bull AnthropolSurv India. 1972;17:439-449.
4. Shrikhande AV, Dani AA, Tijare JR and Agrawal AK. Hematological profile of sickle cell disease in central India. Indian J Hematol Blood Transfus. 2007;23(3):92-98.https://doi.org/10.1007/s12288-008-0005-z
5. Maier-Redelsperger M, De Montalembert M, Flahault A, Neonato MG, Ducrocq R, Masson MP, *et al*., Fetal hemoglobin and f-cell responses to long-term hydroxyurea treatment in young sickle cell patients. Blood. 1998;91(12):4472-4479.
6. Ndefo UA, Maxwell AE, Nguyen H and Chiobi TL. Pharmacological management of sickle cell disease. P T. 2008;33(4):238-243.
7. Agrawal RK, Patel RK, Shah V, Nainiwal L and Trivedi B. Hydroxyurea in sickle cell disease: Drug review. Indian J Hematol Blood Transfus. 2014;30(2):91-96.https://doi.org/10.1007/s12288-013-0261-4
8. Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, *et al*., National institutes of health consensus development conference statement: Hydroxyurea treatment for sickle cell disease. Ann Intern Med. 2008;148(12): 932-938.
9. Jayabose, Somasundaram, *et al*., Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. The Journal of pediatrics 129.4 (1996): 559-565.
10. Silva-Pinto AC, Angulo IL, Brunetta DM, Neves FI, Bassi SC, Santis GC, *et al*., Clinical and hematological effects of hydroxyurea therapy in sickle cell patients: A single-center experience in Brazil. Sao Paulo Med J. 2013;131(4):238-243.https://doi.org/10.1590/1516-3180.2013.1314467
11. Pondugala, Sunil K., *et al*., To assess the efficacy of hydroxyurea, in children with homozygous sickle cell disease, in the age group of 1 year to 18 years, at tertiary care hospital. Journal of Dr. NTR University of Health Sciences 1.4 (2012):227.
12. Deshpande, S. V., *et al*.,Hydroxyurea in sickle cell disease: our experience in Western India. Indian Journal of Hematology and Blood Transfusion 32 (2016): 215-220.