

Clinical outcome and laboratory parameters in sickle cell anemia patients of pediatric age group post hydroxyurea therapy.

Abstract:

Background- Homozygous condition in SCD is called as SCA. In sickle cell anemia patients clinically presents as hemolytic anemia, vaso-occlusive events, along with organ dysfunction and acute chest syndrome. Recently Hydroxyurea has shown promising results in treatment of sickle cell anemia. Hydroxyurea is the only approved drug by FDA which has shown disease modifying results. **Aim-** To determine the clinical outcome and laboratory parameters in SCA patients of pediatric age group post-hydroxyurea therapy. **Methods-** A total of 30 patients who were diagnosed as Sickle cell anemia(SCA) patients in Sickle cell anemia OPD of Pediatric department were included in the study. **Results-** Hydroxyurea therapy is expected to increase HbF% levels and improve the clinical outcome and laboratory parameters in sickle cell anemia patients of pediatric age group.

Key Word: Sickle cell anemia, Hydroxyurea, HbF%.

Introduction:

Homozygous condition in SCD is called as SCA. In sickle cell anemia(SCA) patients clinically presents as hemolytic anemia, vaso-occlusive events, along with organ dysfunction and acute chest syndrome. Overall quality of life in sickle cell anemia patients is poor and usually have early mortality.^{1,2}

In world more than 3,00,000 children in a year born with sickle cell disease, out of these almost 70% originate from Africa³ In India, incidence of sickle cell disease varies from region to region. Lehman & Cutbush in 1952 detected sickle cell gene for the first time among tribal of Nilgiri hills. Since then almost 300 tribal were screened for sickle cell gene and its prevalence varies from 0-35%. In few states like Chhattisgarh, Madhya Pradesh, Maharashtra, Gujrat, and Orissa; it remains as the major public health issue.⁴

Bone marrow transplant remains the only known treatment for Sickle cell anemia. The availability of bone marrow transplant is greatly hampered as there is lack of matching donors, heavy costing of procedure and associated complication of bone marrow transplant.⁵ Transcranial doppler is used to screen children for risk of stroke and also safe blood transfusion has reduced morbidity.⁶

Recently Hydroxyurea has shown promising results in treatment of sickle cell anemia. Hydroxyurea is the only approved drug by FDA which has shown disease modifying results. In 1998 FDA approved use of Hydroxyurea for adult patients and in recent years it has been added in treatment of children as well.⁷ National heart, lung and blood institute has also recommended hydroxyurea use in SCA as early as by 9 months of age.⁸

In past years there were many studies which showed the effect of Hydroxyurea therapy in pediatric patients having SCA. In these studies, patients showed significant rise of HbF% and reduction in painful crises, number of days of hospitalization, number of blood transfusions and acute chest syndrome.⁹ Our study is focused to demonstrate the experience of the use of

Hydroxyurea at AVBRH in SCA pediatric patients and determining its beneficial effects and short term safety.

RESEARCH QUESTION

What is the Clinical outcome and laboratory parameters of SCA patients of pediatric age group post hydroxyurea therapy?

Population(P)-All pediatric patients diagnosed with Sickle cell anemia in sickle cell OPD.

Intervention(I)-Using Hydroxyurea in treatment of SCA.

Comparison(C)-Comparison of laboratory and clinical parameters in SCA pediatric patient pre- and post- hydroxyurea therapy.

Observation/Outcome(O)-Expected outcome is improvement in both clinical and laboratory parameters post hydroxyurea therapy in SCA pediatric patients.

HYPOTHESIS

Hydroxyurea therapy in Sickle Cell Anemia patients of pediatric age group leads to improvement in Clinical outcome and laboratory parameters.

AIM AND OBJECTIVE

Aim:

To determine the clinical outcome and laboratory parameters in SCA patients of pediatric age group post-hydroxyurea therapy.

Objective:

1. **To Evaluate the clinical outcome**, pre- & post-hydroxyurea therapy in SCA patients of pediatric age group.
2. **To Evaluate the laboratory parameters**, pre- & post-hydroxyurea therapy in SCA patients of pediatric age group.
3. **To compare the clinical outcome and the laboratory parameters**, pre- & post-hydroxyurea therapy in SCA patients of pediatric age group.

MATERIALS AND METHODS

Study Design: Cross sectional study.

Duration of study: 6 months after IEC approval.

Place of Study: Department of Pathology in coordination with Department of Pediatrics, Datta Meghe Institute of medical sciences, Acharya Vinod Bhave Hospital, Wardha.

Sample size^[10]: The study will include 30 Sickle cell anemia pediatric patients.

The sample size with desired error of margin was calculated by the formula

$$n = z^2 \alpha / 2. p. (1-p)$$

$$\frac{d^2}{z^2 \alpha / 2}$$

where,

$z^2 \alpha / 2$ is the level of significance at 5% i.e.

95% confidence interval = 1.96

P= prevalence of SCD in Maharashtra = 3.7% = 0.037

d = desired error of margin = 7 % = 0.07

$$n = \frac{1.96^2 \times 0.037 \times (1-0.037)}{(0.07)^2}$$

$$= 27.93$$

= 30 patients needed in study group

Inclusion criteria:

1. SCA patients of pediatric age group (Upto 14 years of age).
2. Pediatric patients who never treated with hydroxyurea previously.

Exclusion criteria:

1. Children with severe malnutrition.
2. Adult patients of >14 years of age were excluded for study.

Toxicity was defined by one or more of the following criteria^[11]:

1. Absolute neutrophil count(ANC) < 2000 x 10⁶/L.
2. Hb < 5gm/dl.
3. Platelet count < 80,000 x 10⁶/L.
4. Serum creatinine > 1.0 mg/dl.

In case toxicity occurs, Hydroxyurea needs to be stopped for at least one week, and once the toxicity is resolved, Hydroxyurea can be started again with a tapered dose of 2.5 mg/kg body weight.

Methodology:

1. Screening and then confirmatory diagnosis of Sickle cell anemia pediatric patients
2. Counselling of parents regarding hydroxyurea therapy, explaining the benefits and possible adverse effects of this therapy
3. Pre hydroxyurea therapy clinical and laboratory data collection related to number of vaso-occlusive crises, vascular complications, number of hospitalizations and blood transfusions
4. Initiation of hydroxyurea therapy with baseline dose and then reaching MTD
5. Regular monitoring for hydroxyurea toxicity; if noted STOP therapy for atleast a week and then restart the therapy by tapering the dose
6. After every 2 weeks evaluate hematological parameters and After 1 month of therapy evaluate HbF level by HPLC

- Note any positive improvement in clinical and laboratory parameters in SCA pediatric patients.

EXPECTED RESULTS:

Hydroxyurea therapy increases HbF%, decreases blood transfusions, days of hospitalization, incidence of acute chest syndrome. It is expected that Hydroxyurea therapy will overall improve clinical outcome and laboratory parameters in sickle cell anemia patients of pediatric age group.

DISCUSSION:

SCD is a hemolytic anemia in which RBCs predominantly have HbS as a result of inheritance of β -globin mutation. β -globin mutation results from one amino acid substitution in β -globin chain of Hb, hence forming Sickle cell Hb(HbS). The amount of HbF is the most important parameter that influences the clinical outcome of sickle cell disease and also is an important predictor of early mortality in pediatric patients having sickle cell disease¹².

In past few years one approach has been taken into consideration, by induction of HbF even after newborn and fetal period. For this many agents have been used but then agent which has shown promise is use of Hydroxyurea. Hydroxyurea has been known for inducing HbF production in SCD patients. Hydroxyurea is used in a titrated dose and its dose is limited by peripheral blood counts mainly by neutropenia, and occasionally by reticulocytopenia and rarely by thrombocytopenia¹⁷.

ZM Al Hawsawi et al in 2008¹¹ conducted their study to demonstrate the use of hydroxyurea in SCD patients. Total 10 patients were considered in study out of them 04 were female and 06 were male. Age of patients range from 05-15 yrs. The study showed that clinical symptoms like ACS and Painful crises were reduced post hydroxyurea therapy. Laboratory parameters showed significant rise in MCV and HbF% post hydroxyurea therapy.

E Papadopoulou et al in 2015¹³ conducted a study on safety and efficacy of hydroxyurea in children and adolescents with sickle/beta-thalassemia. In the study total 13 pediatric patients with S/b-thalassemia were given hydroxyurea for 2 years and during that period the clinical and laboratory parameters were evaluated. The results showed reduction in ACS, Pain crises and days of hospitalization and also showed significant rise in HbF%, MCV, & MCH.

L Tshilolo et al in 2019¹⁴ conducted a study for Hydroxyurea in children with sickle cell anemia in sub-Saharan Africa. In this study total of 635 pediatric patients were included, amongst them 606 completed screening and they were started on hydroxyurea at a titrated dose. The results showed that hydroxyurea helped them in reducing clinical symptoms and improving Hb% and HbF%.

Akinyemi O.D. Ofakunrin et al in 2019¹⁵ conducted a study to evaluated the effectiveness of hydroxyurea in SCA pediatric patients. Total of 54 patients were enrolled in the study. A baseline clinical and laboratory parameters were recorded. Hydroxyurea therapy was given for 1 year. Post hydroxyurea therapy patients showed significant reduction in painful crises 27 (50%) to 2 (2.7%), and ACS6 (11.1%) to 0 (0.0%). There was also reduction in days of hospital stay and requirements of blood transfusion. Also there was raise in HbF% and HCT levels.

Pareek et. al. studies correlation between nephropathy and ophthalmic complications in cases of sickle cell anemia¹⁶. Related studies were reported by Karthik et. al.¹⁷, Sachan et. al.¹⁸, and Verghese et. al.¹⁹. Wasnik et. al. reported a study on evaluation of serum zinc and antioxidant vitamins in adolescent homozygous sickle cell patients in Wardha²⁰. Other related studies were reviewed²¹⁻²⁴.

SCOPE AND LIMITATIONS

Scope:

The study will make an attempt to accurately find the effect of Hydroxyurea on sickle cell anemia patients in reference to its effect on number of hospitalization, blood transfusions, onset of acute crisis and HbF levels. The change in HbF levels will be estimated before the starting of Hydroxyurea and post Hydroxyurea therapy with the help of HPLC.

Limitation:

A triad consisting of proper hydroxyurea dosing, regular follow-up and compliance of patients to medication is a must while evaluating hydroxyurea effects on clinical and laboratory outcome in patients with sickle cell anemia. Lacunae in any of the above mentioned components can put negative impact on the desired results.

REFERENCES:

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010; 376:2018–31.
2. Aygun B, Odame I. A global perspective on sickle cell disease. *Pediatric Blood Cancer* 2012;59:386–90.
3. Diallo D, Tcherna G. Sickle cell disease in Africa. *Curr Opin Hematol* 2002;9:111.
4. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2013;381:142.
5. Powars DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine* 2005;84:363–76.
6. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639–44.
7. National Heart, Lung, and Blood Institute, National Institutes of Health. The Management of Sickle Cell Disease (NIH Publication No. 02-2117), 2002.
8. Charache S, Terrin ML, Moore RD. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995; 332:1317–22.
9. Schechter A, Rodgers G. Sickle cell anemia: basic research reaches the clinic. *New Engl J Med* 1995;332:1372–4.
10. Kirby A, Gebski V, Keech AC. Determining the sample size in a clinical trial. *Med J Aust.* 2002;177:256–7.
11. Al Hawsawi ZM, Turkistani WA. Effect of hydroxyurea in children with sickle cell disease in Saudi Arabia. *Journal of Taibah University Medical Sciences.* 2008 Jan 1;3(2):129-34.
12. World Health Organization. Sickle-cell Anaemia Report by the Secretariat of the Fifty-ninth World Health Assembly A59/9, 2006.

13. Papadopoulou E, Teli A, Theodoridou S, Gompakis N, Economou M. Safety and efficacy of hydroxyurea in children and adolescents with sickle/beta-thalassemia: two-year experience. *Hippokratia*. 2015 Apr;19(2):172.
14. Tshilolo L, Tomlinson G, Williams TN, et al. Hydroxyurea for children with sickle cell anemia in subSaharan Africa. *N Engl J Med* 2019;380:121–31
15. Ofakunrin AO, Oguche S, Adekola K, Okpe ES, Afolaranmi TO, Diaku-Akinwumi IN, Zoakah AI, Sagay AS. Effectiveness and safety of hydroxyurea in the treatment of sickle cell anaemia children in Jos, North Central Nigeria. *Journal of tropical pediatrics*. 2020 Jun;66(3):290-8.
16. Pareek, Aditi, Aditya Khandekar, Sourya Acharya, Pravin Tidake, and Samarth Shukla. "Correlation between Nephropathy and Ophthalmic Complications in Cases of Sickle Cell Anemia: An Entangled Association." *INDIAN JOURNAL OF MEDICAL SPECIALITIES* 10, no. 2 (June 2019): 72–75. https://doi.org/10.4103/INJMS.INJMS_4_19.
17. Pratapa, Karthik, Sourya Acharya, Yash Gupte, and Samarth Shukla. "Acute B Virus Hepatitis with Fulminant Hepatic Failure Precipitating Crisis in Sickle Cell Disease." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 9, no. 3 (January 20, 2020): 173–75. <https://doi.org/10.14260/jemds/2020/40>.
18. Sachan, Ankita Arun, Bhushan. N. Lakhkar, Bhavana B. Lakhkar, and Shivam Sachan. "Is MRI Necessary for Skeletal Evaluation in Sickle Cell Disease." *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH* 9, no. 6 (June 2015): TC8–12. <https://doi.org/10.7860/JCDR/2015/12747.6095>.
19. Verghese, Betty, Sourya Acharya, Aditya Khandekar, Samarth Shukla, and Neema Acharya. "Clinical Profile of Patients of Sickle Cell Crisis in a Rural Tertiary Care Hospital." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 8, no. 42 (October 21, 2019): 3114–18. <https://doi.org/10.14260/jemds/2019/676>.
20. Wasnik, Rina Raibhan, and Nilkanth Ramji Akarte. "Evaluation of Serum Zinc and Antioxidant Vitamins in Adolescent Homozygous Sickle Cell Patients in Wardha, District of Central India." *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH* 11, no. 8 (August 2017): BC1–3. <https://doi.org/10.7860/JCDR/2017/30855.10320>.
21. Garikapati, Amrutha, Sunil Kumar, Anuj Chaturvedi, and Charan Singh Bagga. "Pseudocyst of Pancreas, Rare Crisis in Sickle Cell Disease." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 9, no. 29 (July 20, 2020): 2072–73. <https://doi.org/10.14260/jemds/2020/451>.
22. Panjwani, Vandana, Sachin Daigavane, Sourya Acharya, and Madhumita Prasad. "Sickle Cell Retinopathy (SCR) in a Patient with Sickle Cell Trait - A Rare Case Report." *JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS* 9, no. 28 (July 13, 2020): 2016–18. <https://doi.org/10.14260/jemds/2020/439>.
23. Amale, Amar, Sourya Acharya, Samarth Shukla, and Sameeksha Dubey. "Falciparum Malaria Infection in a Case of Sickle Cell Trait; Unbalancing the Balanced Polymorphism." *INDIAN JOURNAL OF HEMATOLOGY AND BLOOD TRANSFUSION* 29, no. 2 (June 2013): 123–25. <https://doi.org/10.1007/s12288-012-0158-7>.
24. Bhagat, Vijay M., Shubhangi R. Baviskar, Abhay B. Mudey, and Ramchandra C. Goyal. "Poor Health Related Quality of Life Among Patients of Sickle Cell Disease." *INDIAN JOURNAL OF PALLIATIVE CARE* 20, no. 2 (August 2014): 107–11. <https://doi.org/10.4103/0973-1075.132622>.