Real-world HbF status in sickle cell disease from an endemic zone.

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Abstract

Introduction: Sickle cell disease is debilitating hereditary disorder affecting large tribal population in certain parts of India. Complications of sickle cell disease are veno-occlusive crisis, gall stones, leg ulcers, stroke, anemia requiring transfusions adding to the decreasing quality of life. Usage of hydroxyurea increase value of HbF and thereby decreases the complications. To assess the real world scenario of SCD patients, particularly, there levels of HbF, a random clinical examination with blood sampling was initiated and compared to baseline available data. **Methods :** Confirmed cases of sickle cell disease attended special clinical camps. Patients of all age group were invited to attend the camp. To assess the real world scenario of SCD patients, particularly the levels of HbF, a questionnaire and a random clinical examination with blood sampling was initiated and compared to baseline available data. **Results:** One hundred fourteen patients attended the camp. There were 68 males and 46 female patients with a median age group of 19 years (2-70 years). HU was prescribed on average considering age of the patient and average weight. 104 children were taking hydroxyurea. Exact dose calculations were not used. The dose averages between 10 mg/kg to15 mg/kg. As there was only one formulation available , the required daily dosing was changed to fixed dose scheduling There was significant change in the levels of HbF in the patients on hydroxyurea in all age groups using fixed dose combination. **Conclusions:** The achievement of desired HbF target levels using "real-world" scenario, compels us to think about HU strategies. The practice of using fixed dose schedules, in real-time clinical practice, with minimal follow up deserves a serious discussion and could be of great use in low resource countries.

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Abstract

Introduction:

Sickle cell disease is debilitating hereditary disorder affecting large tribal population in certain parts of India. Complications of sickle cell disease are veno-occlusive crisis, gall stones, leg ulcers, stroke, anemia requiring transfusions adding to the decreasing quality of life. Usage of hydroxyurea increase value of HbF and thereby decreases the complications. To assess the real world scenario of SCD patients, particularly, there levels of HbF, a random clinical examination with blood sampling was initiated and compared to baseline available data.

*Methods***:**

Confirmed cases of sickle cell disease attended special clinical camps. Patients of all age group were invited to attend the camp. To assess the real world scenario of SCD patients, particularly the levels of HbF, a questionnaire and a random clinical examination with blood sampling was initiated and compared to baseline available data.

Results:

One hundred fourteen patients attended the camp. There were 68 males and 46 female patients with a median age group of 19 years (2-70 years). HU was prescribed on average considering age of the patient and average weight. 104 children were taking hydroxyurea. Exact dose calculations were not used. The dose averages between 10 mg/kg to15 mg/kg. As there was only one formulation available , the required daily dosing was changed to fixed dose scheduling There was significant change in the levels of HbF in the patients on hydroxyurea in all age groups using fixed dose combination.

Conclusions:

The achievement of desired HbF target levels using "real-world" scenario, compels us to think about HU strategies. The practice of using fixed dose schedules, in real-time clinical practice, with minimal follow up deserves a serious discussion and could be of great use in low resource countries.

Introduction

Sickle cell disease (SCD) disproportionately affects rural population of India. It remains endemic in many states. Morbidity and mortality associated with SCD is well known. This inherited disorder is caused by

formation of HbS. These polymers have the capacity of intravascular polymerization blocking the small vessels , leading to all resultant clinical complications. Complications of the disease like veno-occlusive crisis, chest pain, anemia requiring transfusions add to the decreasing quality of life over time. If there is higher level of HbF, the chances of intravascular polymerization reduce, leading to lesser clinical events and better quality of life. Maintaining higher levels of HbF reduces severity of the disease. Pharmacological intervention like usage of hydroxyurea (HU) induces formation of HbF with resultant increase in its levels. Hydroxyurea has been proven to be most cost-effective intervention. Safety and efficacy of hydroxyurea has been well documented to reduce morbidity and mortality. Long term safety data also have been reassuring. Usage of HU is an internationally recommended standard of care and adopted strategy for the management of sickle cell disease.

Wide variety of programs have been initiated by the governments for hemoglobinopathies, majorly focusing on screening, early detection, screening of pregnant woman. SCD patients are encouraged to visit sickle cell centers where it is a common place practice to initiate hydroxyurea. The system of drug delivery is well designed in few districts. There is no regular follow up of these patients and once initiated hydroxyurea is maintained by patient himself and intervention and corrections are rare. There is no led down care pathway available in the periphery. To assess the real world scenario of SCD patients, particularly there levels of HbF, a random clinical examination with blood sampling was initiated and compared to baseline available data. Objective of this intervention was to understand real world levels of HbF and clinical scenario, requiring presumably lesser clinical interventions.

Methods

114 confirmed cases of sickle cell disease attended special clinical camps. Patients of all age group were invited to attend. Their complete documented and undocumented medical history, available relevant medical information, original Hb analysis reports, were assessed using a questionnaire. Patients were clinically examined, present symptoms, major medical illness, history of pain episodes, transfusions were recorded. History of usage of HU was specifically elucidated. Hemoglobin electrophoresis/High performance liquid chromatography reports from the date of diagnosis (pre-hydroxyurea)were reviewed to study percentage of HbS and HbF. During this camp,89 patients underwent a point of care Hb electrophoresis test (post-hydroxyurea)(Using microchip-based cellulose acetate electrophoresis test) to study present day HbS and HbF levels. Average of Hb S and Hb F levels on the date of diagnosis and present day were calculated and statistically analyzed for significance.

Results

During this exercise ,a total of 114 patients of SCD were reviewed. There were 68 males and 46 female patients with a median age group of 19 years (2-70 years). Majority of patients (n=60) were younger than 20 years.

HU was prescribed on average considering age of the patient and average weight. 104 children were taking hydroxyurea. Exact calculations for dosing were not done. The dose averages between 10 mg/kg to15 mg/kg. As there was only one formulation available , the required daily dosing was changed to fixed dose scheduling , alternate day or five times in seven days, so as to keep the overall dose to near to the planned dose. For example a very young child;3-5 years of age would get about 125 mg per day. A child o 5-10 year would get 250 mg per day (or 500 mg alternate day) and an elder child received 5oo mg/day or 500 mg 5/7 days. Patients were on HU for variable period of time averaging to few years. Dosing modifications were minimal and were done only with change of age .No modifications were done using regular blood reports.

Previous records of Hb electrophoresis were available in 75 patients. The average value of HbS at diagnosis was 67 % and Hb F levels were 20.26 %.A random fresh sampling on the day of examination was done in 98 individuals , it showed an average of 71.91 % Hb S levels (range-46% to 91%) and 27.63 %Hb F levels (range-9- 54%).

For 64 individuals(43 male, 21 female), pretreatment and post treatment data was, available for comparision.

There was considerable time gap between the two readings depending on the age of the patient but was always few years, except in very young patients up to 3 years of age. No difference in report was less than 3 years.

There was no significant change in the levels of HbS between two readings. In age group of patients below 10 years of age, mean +/- standard deviation was 61.89 +/- 17.56 % at the time of diagnosis and 68.09 =/- 8.09 at point of present study, with a p value of 0. 222.In age group of 10-19 years the p value (0.031) was slightly significant. In all other groups HbS values changed insignificantly (Table 1).

HbF levels were also analyzed using available first report and reports performed on the day of this examination. In male population (n=43) the initial Hb F levels were 19.62± 8.0 and present review revealed the levels to be 27.66 ± 8.21, with a p- value of 0.001;In female population (n=21), the initials HbF levels were 21.71±9.30 which increased to 26.09±8.29 ,with p value of 0.005.Both the genders showed significant increase in HbF levels and average level of whole group was always higher than 20 %, range.

HbF levels were compared for various age groups (Table 2). In the age group of 1-10 HbF changed from 20.9 ± 8.68 to 31.90 ± 8.09 , which is statistically significant. In the age group of 10-19 years the value changed from 21.27 ± 8.06 to 26.41±8.16 (p =0.031). Similar changes were observed in all other age groups (Table-1) .In eldest group(age 40years - 49 years) ,interestingly, higher percentile change of HbF was very evident. It changed average from 19.02 ± 6.86 to 35.4±6.80 with significance p-value value of 0.001.

Overall, there was statistically significant increase in the levels of Hb F in all age groups. The Hb F levels lowest recorded were 5.6 % and the highest had gone to 46 %. There was change towards higher side in every single case. The change was evident in all age groups. All patients had reached values higher than 20 % of HbF. The highest values were as high as 46 %

Discussion

The level of Hemoglobin F expression is one of the most important modifiers of sickle cell disease .HbF values influence clinical symptomatology both in children and adults. Increase in value of HbF has been associated with fewer number of veno-occlusive crisis ,fewer episodes of acute chest syndrome and reduced early mortality .

Pharmacological intervention using HU induces HbF production. Hydroxyurea is a recommended treatment strategy in sickle cell disease. Multiple clinical trials have proven its efficacy in reducing morbidity and improving quality of life .

Affordable access to hydroxyurea is well established in state of Odisha in India. In the population we surveyed every patient was taking hydroxyurea more or less regularly, as reported by himself. The delivery is at times hampered because, some patients ,find even the small travel distance unmanageable. Regularity is challenge because of social- patient related issues, which need redressal

HU dosing rationalization (fixed dosing) is standard clinical practice and may defer from recommended dosing guidelines. The criterion of using mild myelosuppression as dosing guide (has never been utilized. Fixed dose HU had been previously reviewed

HUSTLE (NCT00305175) is a prospective observational study with a primary goal of describing the long-term clinical effects of hydroxyurea escalated to maximal tolerated dose (MTD) in children with SCA. In 230 children, providing 610 patient-years of follow up, the mean attained HbF% at MTD was >20% for up to 4 years of follow-up. When HbF% values were [?]20%, children had twice the odds of hospitalization for any reason ($P < .0001$), including vaso-occlusive pain ($P < .01$) and acute chest syndrome (ACS) ($P < .01$), and more than four times the odds of admission for fever ($P < .001$). Therefore, attaining HbF >20% was associated with fewer hospitalizations without significant toxicity. These data support the use of hydroxyurea in children and suggest that the preferred dosing strategy is one that targets a HbF endpoint >20%. According to a 2014 expert panel report sponsored by the National Heart, Lung, and Blood Institute on the evidence-based management of SCA, HU therapy should be offered to all children as young as 9 months of age, regardless of symptom

In this analysis, HbF levels increased in every individual and were more than desired level of 20 %. The change was seen all across population , irrespective of age and gender. In a short group of higher age group the increase in HbF appeared to be even more striking, This observation needs further study and could be result of longer usage of HU, because of higher age group.

The achievement of desired HbF target levels using "real-world" scenario, compels us to think about HU strategies. The practice of using fixed dose schedules, in real-time clinical practice, with minimal follow up deserves a serious discussion and could be of great use in low resource countries. Probably this cohort of real-world scenario proves effectiveness of this strategy which is feasible, manageable, well tolerated , beneficial and covers for the not well trained health personnel.

Conflict of interest

The authors have no financial relationships relevant to this article to disclose. No conflict of interest or funding to declare. All authors have contributed to the manuscript in significant ways, have reviewed and agreed upon the manuscript content

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References

Age group	Number	Pre Hydroxyurea HbS	Post Hydroxyurea HbS	p- value
<10	11	61.89± 17.56	68.09 ± 8.09	0.222 (0.271)
10-19	26	64.42± 11.73	71.88± 8.14	0.031
20-29	13	74.93± 7.61	77.33± 5.78	0.424
30-39	6	73.75± 5.81	70± 6.32	0.224
40-49	5	70.2± 8.18	64.6± 6.80	0.225

TABLE 1- Hb S levels on diagnosis and at point of review

Age group	Number	Pre Hydroxyurea HbF	Post Hydroxyurea HbF	p- value
<10	11	20.9± 8.68	31.90 ± 8.09	0.001
10-19	26	21.37± 8.06	26.41± 8.16	0.012
20-29	13	19.038± 10.78	23.842± 6.98	0.039
30-39	6	20.95± 6.41	30± 6.32	0.024
40-49	5	19.02± 6.86	35.4± 6.80	0.001

TABLE2 HbF levels during initial diagnosis and at the point of review