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Study of Clinical Profile of Vasoocclusive Painful Crisis in Children of Sickle Cell Anemia on Hydroxyurea

[1]Dr. Yogesh Ramdas Chavan and [2]Dr. Jayant Acharya

[1]Department of SNCU, Women District Hospital, Akola, Maharashtra 444001

[2]Department of Paediatrics, Ispat General Hospital, Rourkela (Odisha) 769005

ABSTRACT

Children with sickle cell anemia most often struggle with severe, ongoing discomfort. Most children with sickle cell anemia go through at least one pain crisis year and these crises have a detrimental effect on the kids. Compared to people without pain crises, they are more likely to suffer from despair, a worse quality of life, more frequent absences from school, and strained relationships with their peers. Additionally, as pain crises account for the majority of hospitalizations and emergency department visits among children with sickle cell anemia, they constitute a significant financial and health care services utilization burden. To study the clinical profile of Vaso-occlusive painful crisis in children diagnosed with sickle cell anemia on hydroxyurea. This is an Observational cross-sectional study and the study Duration was from January 2021 to June 2022. The total Sample Size was 48 patients. In our study it was observe that 24(50%) out of 48 children were started on hydroxyurea within one year of admission. Whereas 17 (35.4%) children were on hydroxyurea since >3 years. In those groups who were on hydroxyurea less than 1 year, majority were below 5 year of age 5(100%). The p value (p=0.0075) was statically significant. Hydroxyurea therapy effectively reduces the frequency and severity of VOC in children with SCA, leading to improved quality of life and clinical outcomes. Early initiation of hydroxyurea and close monitoring of therapy adherence are critical in managing SCA in paediatric populations. Further longitudinal studies are recommended to assess long-term benefits and potential side effects.

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Key Words
Painful, sickle cell, anemia, hydroxyurea

Corresponding Author
Dr. Yogesh Ramdas Chavan, Department of SNCU, Women District Hospital, Akola, Maharashtra 444001

Author Designation
[1]Medical officer
[2]Executive Director

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INTRODUCTION

Nearly 20 million sickle cell anemia sufferers reside in India. Among India, the sickle cell gene was initially identified among South Indian tribal tribes and is now well known, particularly in the country's central regions. According to reports, Orissa has the highest sickle cell gene frequency in India, followed by Assam, MP, UP, Tamil Nadu and Gujarat[1].

In Orissa, the prevalence of sickle cell anemia can reach 9.1%, whereas the average in India is 4.3%. The most prevalent symptom of sickle cell anemia is periodic periods of intense pain called Vaso occlusive pain crises, which have a negative effect on the patient's and their caregivers' quality of life. There is significant inter-patient variation in the incidence and intensity of vasoocclusive pain crises in adults with sickle cell anemia[2].

Children with sickle cell anemia most often struggle with severe, ongoing discomfort. Most kids with sickle cell anemia go through at least one pain crisis year and these crises have a serious detrimental effect on kids. Compared to people without pain crises, they are more likely to suffer from despair, a worse quality of life, more frequent absences from school, and strained relationships with their peers. Additionally, as pain crises account for the majority of hospitalizations and emergency department visits among children with sickle cell anemia, they constitute a significant financial and health care services utilization burden[3].

Hydroxyurea can be used to lessen the frequency of pain crises. Which is a drug that raises the blood's level of fetal hemoglobin., hence, higher fetal hemoglobin lowers the risk of red blood cell sickling. When compared to not using hydroxyurea medication, children with sickle cell anemia who get it report fewer early repeated bouts of discomfort, hand-foot syndrome, acute chest syndrome and hospitalization[4].

Children with sickle cell anemia continue to have poor rates of hydroxyurea medication start and adherence, despite the better clinical and financial results of this treatment. Little is known about the traits of children with sickle cell anemia that may influence the initiation of hydroxyurea therapy, despite previous research showing that only roughly half of children receiving hydroxyurea based on clinical indication have at least one filled prescription., among those already receiving hydroxyurea therapy, hydroxyurea prescriptions only cover roughly half of the year[5].

MATERIALS AND METHODS

Type of Study: Observational cross-sectional study.

Place of study and Duration: from January 2021 to June 2022.

Sample Size: 48 patients.

Inclusion: All known case of sickle cell anemia on hydroxyurea who are admitted for painful episode were included.

Exclusion

- Pre-existing co-morbid condition (e.g., nephrotic syndrome, chronic kidney disease, diabetic mellitus type 1, malignancy and cyanotic heart diseases) .
- Sickle cell disease with end organ damage.
- Admitted for pain but for other than Vaso-occlusive painful crisis.
- Patient who refuses to be a part of study.
- Patient on chronic medication other than hydroxyurea (e.g., antiepileptic, steroid, antileukemic drug and insulin).
- Mean+S.D.
- Using proper statistical paired and unpaired test.
- ANOVA Test 4) Correlation was done by Pearson's methods.

Statistical Analysis: For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0., SPSS Inc., Chicago, IL, USA) and Graph Pad Prism (version 5). Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests, which compare the means of independent or unpaired samples, were used to assess differences between groups. Paired t-tests, which account for the correlation between paired observations, offer greater power than unpaired tests. Chi-square tests (χ^2 tests) were employed to evaluate hypotheses where the sampling distribution of the test statistic follows a chi-squared distribution under the null hypothesis., Pearson's chi-squared test is often referred to simply as the chi-squared test. For comparisons of unpaired proportions, either the chi-square test or Fisher's exact test was used, depending on the context. To perform t-tests, the relevant formulae for test statistics, which either exactly follow or closely approximate a t-distribution under the null hypothesis, were applied, with specific degrees of freedom indicated for each test. P-values were determined from Student's t-distribution tables. A p-value ≤ 0.05 was considered statistically significant, leading to the rejection of the null hypothesis in favour of the alternative hypothesis.

RESULTS AND DISCUSSIONS

As can be seen from the above table, the most common complaint among children under the age of five and those aged five to ten was stomach discomfort, which accounted for 4 (80%) and 8 (44.4%) of the total complaints. It was intriguing to see,

Table 1: Distribution of What is the Major Chief Complaint of the Child on Hydroxyurea? And did the Child Take Hydroxyurea Before Vaso-Occlusive Crisis?

		AGE				
		<5Year [n=5]	5-10 Year [n=18]	>10 Year [n=25]	[N=48]	P-value
Chief Complaint	Abdominal Pain	4(80%)	8(44.4%)	8(32%)	20(41.6%)	0.4963
	Back Pain	0(0%)	0(0%)	5(20%)	5(10.4%)	
	Chest Pain	0(0%)	2(11.1%)	2(8%)	4(8.3%)	
	Joint Pain	1(20%)	6(33.3%)	10(40%)	17(35.4%)	
	Leg Pain	0(0%)	2(11.1%)	0(0%)	2(4.1%)	
	Total	**5(100%)**	**18(100%)**	**25(100%)**	**48(100%)**	
Drug Compliance	1* (Continue Drug)	4(80%)	17(94.4%)	22(88%)	43(89.5%)	0.1382
	2a (Stop drug<7 day)	1(20%)	0(0%)	0(0%)	1(2%)	
	2b(Stop drug >7 day)	0(0%)	1(5.5%)	3(12%)	4(8.3%)	
	Total	**5(100%)**	**18(100%)**	**25(100%)**	**48(100%)**	

Table 2: Distribution of What is the Severity of Anemia During Vaso-Occlusive Painful Crisis? And Did the Child have Dehydration During Vaso-Occlusive Crisis?

		AGE				
		<5 Year [n=5]	5-10 Year [n=18]	>10 Year [n=25]	[N=48]	P-value
Anemia (gm/dl)	Mild (Hb>10)	1(20%)	3(16.6%)	5(20%)	9(18.7%)	0.9713
	Moderate (Hb8-10)	1(20%)	7(38.8%)	11(44%)	19(39.5%)	
	Severe (Hb<8)	3(60%)	8(44.4%)	9(36%)	20(41.6%)	
	Total	**5(100%)**	**18(100%)**	**25(100%)**	**48(100%)**	
Dehydration	No	3(60%)	16(88.8%)	23(92%)	42(87.5%)	0.3292
	Some	2(40%)	1(5.5%)	2(8%)	5(10.4%)	
	Severe	0(0%)	1(5.5%)	0(0%)	1(2%)	
	Total	**5(100%)**	**18(100%)**	**25(100%)**	**48(100%)**	

Table 3: Distribution of What are the Factors Affecting Outcome of the Hospital Stay?

Factor Affected on Outcome		<3 Day	3-5 Day	>5 Day	P-Value
Age	<5 Year	0(0%)	5(18.5%)	0(0%)	0.3285
	5-10 Year	1(33.3%)	10(37%)	7(38.8%)	
	>10 Year	2(66.6%)	12(44.4%)	11(61.1%)	
B] Pain Intensity	Moderate	1(33.3%)	7(25.9%)	6(33.3%)	0.8548
	Severe	2(66.6%)	20(74%)	12(66.6%)	
C] Dose of Hydroxyurea	<20 Mg/Kg	1(33.3%)	15(55.5%)	9(50%)	0.7466
	>20Mg/Kg	2(66.6%)	12(44.4%)	9(50%)	
D] Duration of Hydroxyurea	<1 Year	1(33.3%)	13(48.1%)	9(50%)	0.8575
	1-3 Year	1(33.3%)	3(11.1%)	3(16.6%)	
	>3 Year	1(33.3%)	11(40.7%)	6(33.3%)	
E] Drug Compliance	1*(Continue drug)	3(100%)	23(85.1%)	17(94.4%)	0.8112
	2a*(Stop drug <7 day)	0(0%)	1(3.7%)	0(0%)	
	2b*(Stop drug>7 day)	0(0%)	3(11.1%)	1(11.1%)	
E] Duration of Pain at Admit	<1 Day	1(33.3%)	2(7.4%)	7(38.8%)	0.1303
	1-2 Day	1(33.3%)	11(40.7%)	6(33.3%)	
	>2 Day	1(33.3%)	14(51.8%)	5(27.7%)	

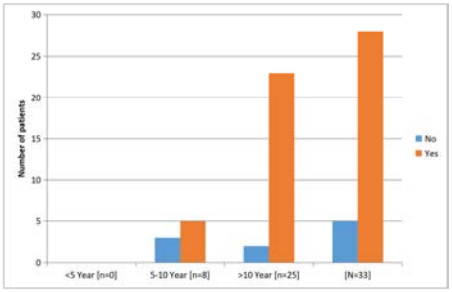

Fig. 1: Distribution of Can Child with Sickle Cell Crisis Attends the School?

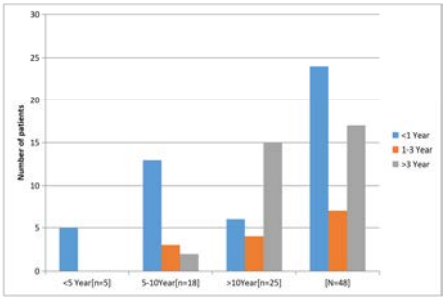

Fig. 2: Distribution of How Many Years Did the Child Take Hydroxyurea?

nevertheless, that the majority of youngsters older than 10 years old (40%) reported having joint discomfort. In our study, we found that only one kid under the age of five stopped using hydroxyurea for fewer than seven days and one child between the ages of five and ten stopped taking the medication for more than seven days. According to the preceding statistics, 20 (41.6%) of the 48 children had severe anemia (Hb<8).It was intriguing to see that children under the age of five had a higher frequency of severe anemia (3, or 60%). The p-value was statistically not significant (p=0.9713). Of the 48 youngsters in our research, 42 (87.5%) did not exhibit any signs of dehydration at the time of admission. Just one child (5.5%) in the 5-10 age range suffers from severe dehydration. There was no statistical significance in the p value (p=0.3292). Across all age groups, the average length of hospital stay was three to five days. The average length of hospitalization for the majority of children across all age groups was three to five days and comparable patterns were observed in the degree and duration of pain, dosage, duration and hydroxyurea medication

compliance. Association of Duration of Hosp Stay with AGE was not statistically significant (p=0.3285). Association of Duration of Hosp Stay with Pain Intensity was not statistically significant (p=0.8548). Association of Duration of Hosp Stay with Dose of Hydroxyurea was not statistically significant (p=0.7466). Association of Duration of Hosp Stay with Duration of Hydroxyurea was not statistically significant (p=0.8575). Association of Duration of Hosp Stay with Drug Compliance was not statistically significant (p=0.8112) and Association of Duration of Hosp Stay with Duration of Pain at Admit was not statistically significant (p=0.1303) In the table above, it was noted that 5 (62.5%) of 8 children in the age category of 5-10 years had missed school because of discomfort. It was also noteworthy to note that 23 (92%), out of 25, had missed school for more than 10 years for the same reason. There was no statistical significance in the p value (p=0.1285). 24 (50%) of the 48 youngsters in our research began using hydroxyurea within a year of their admission. However, 17 youngsters (35.4%) have been on hydroxyurea for more than three years. In those group who were on hydroxyurea less than 1 year, majority were below 5 year of age 5(100%). The p value (p=0.0075) was statically significant.

In our study, it was observed that the majority of children were above 10 years of age in comparison to those who were below 10 years and was statistically significant(p<0.05). Similar observation was also reported by Barma[6].

Moreover, the studies done on SCD in children by Charache S *et al* (1995) showed a female preponderance[7], Similar observation was also observed in our study, though not statistical significance.

Many Indian studies e.g., Kate SL *et al* (2002), Awasthy N *et al* (2008), Verghese[8] on sickle cell Joint pain is the most prevalent presentation in children with sickle cell disease, with hip, non-articular and knee joint pain occurring in decreasing order of frequency. However in our study, majority of children 40%(N=48) of the study population presented with pain in ankle joint followed by knee and hip joint respectively in children who were >10 year. However, it was interestingly to observed in our study that in those children who were less than 10 years the major presented symptom was abdominal pain (non-articular), which was not statistically significant in that age group.

According to earlier research on sickle cell illness conducted by Valeska Brito da Cunha *et al.* in 2020, all children, regardless of age, experienced moderate to severe pain that was managed at home using non-systemized, unplanned and efficient analgesics. Although not statistically significant, the study we conducted found that younger people had more intense pain. A delayed diagnosis, a delayed start of hydroxyurea, or parents' ignorance of their children's pain levels might be the cause.

Aditi Pareek *et al* in 2019 had reported that upper respiratory tract infection in children of sickle cell disease had major contributory factor in precipitating painful crisis[9]. Similar findings were also seen in our study, which found that 42.8% of the study group had an upper respiratory tract infection prior to the distressing hospitalization of children. Additionally, we found that a rise in physical activity over a ten-year period was a contributing factor to comparable events. Study done by Walsh KE *et al* in2014 reported that sickle cell children on hydroxyurea who were admitted for painful crisis were non-compliance to Hydroxyurea therapy[10]. However, it was intriguing to see that 43 out of 48 children in our research continued to use drugs, which may have been caused by the caregivers' explanations of the drug's advantages and safety to the parents.

Sickle cell Pain crisis was one of the major reasons for absenteeism from school as reported by Valeska Brito da Cunha et al in 2020 in the study done in Brazil[11]. Similar observation was also done in our study though not statistically significant (p<0.1285).

The frequency of painful crisis was observed to be more in children >20 year in the studies done by Diop et al in 2003 in Dakar, Senegal (West Africa). Many Indian reports have also suggested that majority of children were having history of pain crisis in past[12], In our observation it was seen that 72% children above 10 years had greater than 2 episodes of painful crisis, in a year., though not statistically significant (p=0.1658). Possibly due to less number of children included during the study period.

Regardless of the age upon admission, the mean hemoglobin level in a 2019 research by Verghese B *et al.* in Wardha, India, was <5 gm/dl during the excruciating crisis of children with sickle cell disease. However, it was intriguing to note that the mean hemoglobin level in children under 10 years old was <8 gm/dl, whereas the mean hemoglobin level in children over 10 years old was 8-10 gm/dl. Delays in diagnosis and, consequently, in starting hydroxyurea treatment might be the reason for the higher prevalence of moderate to severe anemia in the younger age group.

It was also observed in our study that all children of sickle cell disease who were admitted for painful crisis, were very consistent for continuation of Hydroxyurea therapy, in contrast to the reports published by Anders DG et al in 2016 in New York State in 273 children, whereas the use of Hydroxyurea was only 56.3% of the study population[13]. The difference in this practice may be due to increased awareness by the parents,

explained by the caregivers regarding the advantage of hydroxyurea to prevent such complication in sickle cell disease.

Nevertheless, our study also found that while hydroxyurea as a medication offers general advantages for these kids, such as reducing the risk of subsequent Vaso occlusive episodes and the need for transfusions, it had no discernible impact on the average length of hospitalization or its results.

CONCLUSION

Comparing several research conducted in India and other parts of the world, we came to the conclusion that painful sickle cell disease crises were more prevalent in women than in men. Increased physical activity and upper respiratory tract infections were the main causes of the widespread abdominal involvement. For Hydroxyurea, drug compliance was excellent. Due to terrible crises, the majority of youngsters continue to miss school. In times of stress, the majority of them suffer from mild to severe anemia. The average length of hospital stay and its result were not significantly impacted by hydroxyurea.

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