Original Article

Assessment of Cognitive Functioning and Quality of Life in Sickle Cell Anaemia Patients Taking Hydroxyurea in Central India

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ABSTRACT

Aim and Objectives : To assess and compare disease specific quality of life using SCD-QoL questionnaire and cognitive functioning using MMSE in SCD pediatric patients taking hydroxyurea and those not taking hydroxyurea.

Methods : Total 60 SCD patients of either sex, ages between 13-18 years were included in the study and were divided into hydroxyurea group and non-hydroxyurea group of 30 patients in each group. Patients having Hb-SS pattern and who completed Sickle cell disease quality of life questionnaire and mini mental state exam (MMSE) questionnaire during their visit to GMC, Nagpur were included in the study. Graph Pad prism 5.01 was used for statistical analysis.

Results : The mean age of patients on hydroxyurea was 15.96 ± 1.535 years while those not taking hydroxyurea was 16.68 ± 1.832 years. Significantly higher MMSE summary score was seen in (28.23 ± 1.278) SCD patients on hydroxyurea treatment. No significant difference was seen between the two groups in terms of overall SCD-QoL score.

Conclusions : No beneficial effect on disease specific quality of life has been observed in hydroxyurea group. Hydroxyurea has beneficial effect on cognition although the mechanisms by which hydroxyurea may improve cognitive outcomes is not clear which warrants further clinical trial in this regard.

Keywords : Sickle cell anemia; Quality of life; Hydroxyurea, Mini mental state exam

Introduction :

Sickle cell disease (SCD) is the most common inherited red blood cell (RBC) disorder affecting hemoglobin. Sickle cell disease patients may suffer from different complications like vaso-occlusive crises, haematological and infectious crises, strokes, retinopathy, leg ulcer growth retardations etc. Health-related quality of life (HQOL) is a multidimensional concept that includes the physical, emotional, and psychosocial components associated with a disease or its treatment[1] in different domains of life, addressing the patients' perceptions of their situations. Increasing self-reported satisfaction in the domains of life is associated with higher levels of quality of life. Improving HQOL has become an important objective of medical care[2-4]. However the measurement of health-related quality of life (HQOL) in sickle cell patient may help doctor to find problem area of the therapy. Most of the studies on quality of life in sickle cell patient have been conducted in economically developed countries while limited amount of data exists from developing countries.

Hydroxyurea (HU), a myelosuppressive agent which is used in an off-label manner for treatment of sickle cell anemia in children and it benefits the patient by improving fetal hemoglobin (HbF) parameters[5]. Also, it is used to decrease the crises in patient of sickle cell disease[6]. Majority of studies conducted in the past regarding safety and efficacy of hydroxyurea in sickle cell anemia have well established its role in improving laboratory parameters and reducing frequency of sickle cell crisis. Previous studies have shown association of sickle cell disease with cognitive impairment due to frequent cerebrovascular events (CVEs)[7]. The impact of hydroxyurea therapy on cognitive function in patients with sickle cell disease is not well understood although sequel of CVEs can adversely impact their quality of life. In one

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comparative study involving adults with SCD, hydroxyurea showed better HbF response which resulted in improvement in HRQL in those receiving hydroxyurea compared to those not on hydroxyurea treatment[8]. Similarly one study reported improvement in HRQL with better social functioning in asymptomatic children with SCD who were started on hydroxyurea to prevent chronic organ damage[9].

However extremely scarce data is available regarding quality of life in children with SCD who are receiving hydroxyurea therapy compared to children with SCD who are not receiving this therapy. So this study was planned to assess and compare the quality of life and cognitive functioning among patients taking hydroxyurea versus those not taking hydroxyurea.

Materials and Methods :

This was a cross sectional study enrolling total 60 SCD patients of either sex, age between 13 to 18 years. They were divided in two equal groups i.e. Hydroxyurea and non-hydroxyurea group. After obtaining Institutional Ethics Committee approval and written informed consent from patients / legal guardians study was started. Patients having Hb-SS pattern, who completed sickle cell disease quality of life questionnaire and mini mental state exam (MMSE) questionnaire during their visit to GMC, Nagpur were included in the study. The above study population represents a convenience sample of children suffering from SCD. Patients taking hydroxyurea for more than 1 year were included in the hydroxyurea group while those taking hydroxyurea intermittently were excluded from the study. Demographic data was obtained from the child's medical record. The duration of hydroxyurea therapy was calculated when applicable.

For assessing the quality of life we used sickle cell disease quality of life questionnaire (SCD-QoL) containing 28 items and scores ranged from 1= Always to 4= Never, with higher scores representing higher quality of life[10]. The MMSE is a popular instrument developed in 1975 as a brief tool to measure global cognitive function, to track cognitive changes that occur with time, and to assess the effects of drugs on cognitive functioning. MMSE consists of nineteen items on orientation, registration, attention and calculation, recall, language, praxis has score from 0 to 30. Scores below 24 commonly indicate a cognitive deficit[11]. The data about the quality of life and cognitive function was obtained from both the groups and was compared using appropriate Graph Pad Prism Version 5.01.

Statistical Analysis : Descriptive statistics were summarized by means and standard deviations for continuous variable and number and percentage for categorical variables. Unpaired "t" test and Mann Whitney U test were used to compare parametric and non parametric quantitative variables respectively. A P-value of < 0.05 was considered statistically significant.

Observations and Results :

The mean age of patients in hydroxyurea group was 15.96 ± 1.535 years while those not taking hydroxyurea was 16.68 ± 1.832 years. There was no statistically significant difference observed in both the groups in terms of age. Most patients were taking hydroxyurea for less than 5 years and the average duration at the time of assessment of hydroxyurea treatment was 4.8 ± 3.537 years. Reasons for starting hydroxyurea included recurrent vaso-occlusive pain, recurrent hospital admissions, recurrent or single episode of life threatening ACS. Majority of patients (30%) in hydroxyurea group were diagnosed with sickle cell disease early in their life (< 1 year) while most patients not taking hydroxyurea (50%) were diagnosed late (between 5-10 years of their life). More number of patients in non-hydroxyurea group, missed school for duration more than 3 months. However overall comparison between two groups showed no significant difference in days missed due to disease activity. In both the groups, majority of patients reported to hospital for routine checkup followed by for complaint of pain. Most patients belonged to Scheduled caste especially Mahar sub caste in both groups ***(Table 1).***

MMSE scores for subcategories including orientation to time, orientation to place and recall in

SCD patients on hydroxyurea treatment were significantly higher compared to non-hydroxyurea SCD patients group. Similarly significantly higher MMSE summary score was seen in SCD patients on hydroxyurea treatment. For other MMSE categories, there was no difference observed between two groups ***(Table 2).***

As show in ***Table 3*** no significant difference was seen between two groups in terms of overall SCD-QoL score, however significantly lower emotional score in SCD patients taking hydroxyurea was observed. Other subscales of SCD-QoL showed no statistical difference between two groups.

Discussion :

From the results of our study it is clear that in both the groups more number of SCD patients of Scheduled caste category (Mahar subcategory) were affected. Similar results were also observed in one epidemiological study of SCD in central India by Kamble et al[12]. More educational programs for creating awareness about SCD are required in this region for people in Scheduled caste with better pre-marriage and post marriage counseling about SCD simultaneously[13].

The primary objective of our study was to assess and compare the disease specific quality of life in

Table 1 : **Various characteristics of sickle cell disease patients**

Characteristics		Hydroxyurea Group	Non-hydroxyurea Group
Gender	Male	17 (56.67%)	17 (56.67%)
	Female	13 (43.33%)	13 (43.33%)
Family Members	≤4 members	17 (56.67%)	17 (56.67%)
	5 members	9 (30%)	8 (26.67%)
	≥6 members	4 (13.33%)	5 (16.67%)
Purpose of visit to hospital	Routine checkup	18 (60%)	14 (46.67%)
	Pain	10 (33.33%)	11 (36.67%)
	Other	2 (6.67%)	5 (16.67%)
Religion / Caste	Scheduled Caste	23 (76.67%)	19 (63.33%)
	Scheduled Tribe	3 (10%)	2 (6.67%)
	Other Backward Class	4 (13.33%)	9 (30%)
Age at diagnosis	□ 1 year	9 (30%)	4 (13.33%)
	Between 1-4 years	9 (30%)	6 (20%)
	Between 5-10 years	5 (16.67%)	15 (50%)
	Between 11-16 years	7 (23.33%)	5 (16.67%)
Hydroxyurea Treatment duration	≥1 year	7 (23.33%)	-
	≥2-≤5 years	15 (50%)	-
	≥5-≤9 years	3 (10%)	-
	≥10 years	4 (13.33%)	-
School Missed due to crisis	≤1 month	17 (56.67%)	19 (63.33%)
	≥1 month-≤3 months	12 (40%)	5 (16.67%)
	> 3 months	1 (3.33%)	6 (20%)
Hemoglobin level	< 6 gm%	5 (16.67%)	8 (26.67%)
	> 6-≤8 gm%	11 (36.67%	6 (20%)
	> 8-≤10 gm%	11 (36.67%)	14 (46.67%)
	> 10 gm%	3 (10%)	2 (6.67%)

Table 2 : **MMSE results in patients taking hydroxyurea vs not taking hydroxyurea**

MMSE Categories	Hydroxyurea Group	Non-hydroxyurea Group	P value
Orientation to time	4.86 ± 0.34	4.1 ± 1.094	□ 0.001
Orientation to place	4.86 ± 0.34	4.133 ± 1.008	□ 0.01
Registration	3 ± 0	3 ± 0	NS
Attention and calculation	4.23 ± 0.93	3.6 ± 1.453	NS
Recall	2.7 ± 0.59	2.333 ± 0.7112	□ 0.05
Naming	2 ± 0	1.933 ± 0.25	NS
Repetition	0.933 ± 0.25	0.966 ± 0.18	NS
3 stage command	3 ± 0	2.8 ± 0.66	NS
Complex commands (read and obey)	1 ± 0	0.9 ± 0.30	NS
Complex commands (write a sentence)	0.96 ± 0.18	0.833 ± 0.37	NS
Complex commands (copy of pentagon)	0.66 ± 0.47	0.633 ± 0.49	NS
MMSE summary score	28.23 ± 1.27	25.23 ± 2.73	□ 0.0001

MMSE - Mini Mental State Examination scale; NS - not significant; statistical test used Mann-Whitney U test

Table 3 : **Sickle cell disease quality of life (SCD-QoL) scores**

SCD-QoL Subscales	Hydroxyurea group	Non-hydroxyurea group	P value
Physical score	16.87±3.91	17.27±4.06	NS
Emotional score	18.23±3.287*	19.9±3.34	0.0372
Social score	19.23±3.36	19.2±2.44	NS
School score	13.13±2.11	13.97±1.93	NS
Overall score	73.97±9.90	77.17±8.92	NS

patients taking hydroxyurea Vs those not taking hydroxyurea. The overall quality of life score measured in hydroxyurea group was not significantly different from those not receiving hydroxyurea. Many previous studies have confirmed the finding that overall health-related quality of life among SCD patients is significantly lower as compared with patients suffering from other non-communicable diseases[8,14,15]. Significant improvement in the quality of life was observed over 2 years in SCD patients receiving hydroxyurea compared with receiving placebo. The patient in the hydroxyurea group showed high Hb F response. The benefits were restricted to certain aspects of HRQL[8]. However in our study no such difference seen between the two treatment groups. In fact our study demonstrated significantly lower emotional score in patients receiving hydroxyurea compared to those not receiving hydroxyurea. Such controversial finding might be due to chronic fatigue and small physical size, which may adversely affect social functioning of male with SCD leading to aggressive behavior and in females with SCD due to difficulty in development of normal social relationships. Controversial reporting of lack of demonstrable effects of hydroxyurea on quality of life measures obtained in our study might be due to the result of issues inherent in the process of selection for the patients with moderate-to-severe disease who were already debilitated and had irreversible effects of their disease. In our study, patient belonging to Hydroxyurea group were diagnosed early in their life as compared to non-hydroxyurea group. Hence because of long standing disease and frequent complications of the disease compared to those with mild to moderate disease and not on hydroxyurea, quality of life score might not be significantly different between the two groups or there might be a possibility that patients receiving hydroxyurea had stable quality of life score.

The overall MMSE score in our study was significantly higher in SCD patients taking hydroxyurea compared to those not taking hydroxyurea. Thompson et al[16] reported disease related differences in cognitive functioning in children as young as 2 years old, showing that neurocognitive decrements can occur early and often before any other severe complications of SCD have been observed. The findings of improved MMSE scores in present study provide preliminary evidence to support the hypothesis that hydroxyurea may improve cognitive functioning. Results showed that hydroxyurea therapy was related to higher scores of MMSE subscale like orientation, recall and also overall MMSE score. The benefits of hydroxyurea on cognitive function improvement might be due to factors that could be impacted by hydroxyurea such as direct effects of anemia and vasoocclusion on brain function, or indirect effects on cognitive performance through fatigue or reduced learning opportunities. Similar findings were observed in a study by Puffer et al where cognitive abilities of 15 children with SCD on hydroxyurea were compared to 50 other children with SCD, controlling for demographics and hematocrit and children on hydroxyurea scored significantly higher on cognitive scores[17].

Conclusion :

Hydroxyurea has beneficial effect on cognition although the mechanisms by which hydroxyurea may improve cognitive outcomes is not clear. It will be interesting to know whether hydroxyurea may act to reverse existing cognitive decrements or only to prevent future cognitive decline understanding the impact of hydroxyurea on cognitive abilities and quality of life will lead to more informed treatment decisions for children with SCD. However the findings of present study provide a strong rationale for future studies on the cognitive benefits of hydroxyurea treatment. Many previous studies have shown beneficial effects of hydroxyurea on quality of life of SCD patients, such findings were not observed in our study. Future prospective long term studies are needed in this regard with large sample size with stringent patient selection criteria.

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