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DIFFERENCES IN HEALTH RELATED QUALITY OF LIFE IN CHILDREN WITH SICKLE CELL DISEASE RECEIVING HYDROXYUREA

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Abstract

Hydroxyurea is a safe and efficacious medication for children with sickle cell disease (SCD). Our objective was to compare health related quality of life (HRQL) between children taking hydroxyurea and those not taking hydroxyurea. We conducted a retrospective cohort study of children with SCD who had completed the PedsQL 4.0 at Duke University Medical Center or the Midwest Sickle Cell Center. Our primary outcome was HRQL in children receiving hydroxyurea therapy compared to those not receiving hydroxyurea. One hundred ninety-one children with SCD were included in the study. Children in the hydroxyurea group had higher self-report Total Peds QL median scores than children in the no hydroxyurea group; p=0.04. Child self-report physical functioning scores were significantly higher for children in the hydroxyurea group; p=0.01. In conclusion, children with SCD who are receiving hydroxyurea therapy report better overall HRQL and better physical HRQL than children not receiving this therapy despite disease severity. Further research assessing the impact of hydroxyurea therapy on HRQL, such as prospective assessment over time, would aid in our understanding of the effectiveness of hydroxyurea for individual children. Ultimately, this may aid in decreasing the barriers to the use of hydroxyurea.

Keywords

sickle cell disease; hydroxyurea; health related quality of life

INTRODUCTION

Health related quality of life (HRQL) is an important patient reported outcome measure for children[1,2] and aids in our understanding of the well being of children with sickle cell disease (SCD). Children with SCD have lower baseline HRQL than healthy controls[3–5] and those children with severe disease have worse HRQL than those with milder disease. Furthermore, HRQL worsens during acute vaso-occlusive painful events.[6]

Little is known about the effect of disease modifying therapy on the well being of a patient with SCD. Hydroxyurea is the only medication used to ameliorate acute and chronic

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complications of SCD.[7–9] In adults who participated in the Multicenter Study of Hydroxyurea, HbF response was associated with improvement in HRQL in those receiving hydroxyurea.[10] Thornburg et al. recently reported stable HRQL and decreased impact of disease on family functioning in 14 young, asymptomatic children with SCD who were started on hydroxyurea to prevent chronic organ damage.[11] However, there are no data on the HRQL of children with SCD who are receiving hydroxyurea therapy compared to children with SCD who are not receiving this therapy. Further evaluation of the impact of hydroxyurea on HRQL is warranted.

The objective of this study was to examine differences in HRQL between children with SCD who were receiving hydroxyurea therapy and those who were not receiving this disease modifying therapy. We hypothesized that HRQL would be better in those children receiving hydroxyurea therapy regardless of disease severity.

MATERIALS AND METHODS

Study Setting and Subjects

This was a cross sectional, retrospective study of children with SCD. Two groups of children ages 2–18 years met eligibility for this study: 1) Children who were in their baseline state of health and had completed the PedsQL 4.0 generic core scales during a routine clinic visit at the Midwest Sickle Cell Center Clinic in Milwaukee, Wisconsin; and 2) Children with SCD who were in their baseline state of health and had completed the PedsQL 4.0 generic core scales during a routine clinic visit to Duke University Medical Center. The study population represents a convenience sample of children. Children on chronic transfusion therapy were excluded from the analysis because transfusions are disease modifying therapy and there were too few subjects receiving transfusions to make valid comparisons to other groups.

Measurements

Demographic data were parent-reported or obtained from the child's medical record. Data were abstracted from the medical record to determine if the child was on hydroxyurea at the time that the HRQL instrument was completed. The duration of hydroxyurea therapy was calculated when applicable. To determine disease severity, clinical data were abstracted from the medical record. Children were classified as having severe disease if they had ever had stroke or acute chest syndrome (ACS) prior to completing the PedsQL and/or if they had 3 or more hospitalizations for vaso-occlusive pain in the prior three years.[2,12–14] All other children were classified as having mild disease.

Primary Outcome

The primary outcome was HRQL measured with the PedsQL™ generic core scales parent-proxy and child self-report questionnaire. The PedsQL™ is a 23 item generic HRQL questionnaire that has a parent-proxy report for children ages 2 through 18 years and a child self-report questionnaire for children ages 5 to 18 years.[15] The questionnaire yields information on the physical, emotional, social and school functioning of the child during the previous 4 weeks. It has been extensively tested in healthy children,[16,17] children with chronic disease,[18–21] and has been validated and found to be reliable in children with SCD.[22,23] Mean scores are calculated based on a 5-point response scale for each item and transformed to a 0 to 100 scale with a higher score representing better quality of life. There are 4 scale scores: physical functioning, emotional functioning, social functioning, and school functioning. In addition, the PedsQL™ yields 3 summary scores: a total scale score, a physical health summary score, and a psychosocial health summary score. The total score is comprised of the average of all items in the questionnaire. The psychosocial summary score

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is comprised of the average of the items in the emotional, social, and school functioning scales. The physical health summary score is comprised of the average of items in the physical functioning scale and is the same as the physical functioning scale score. Missing items were handled based on the developer's recommendation which allows a scale score to be calculated if at least 50% of the items in each scale are answered.[15]

The Institutional Review Boards of Duke University Medical Center and the Children's Hospital of Wisconsin/Medical College of Wisconsin approved the study and informed consent was obtained from the parents and assent from the children where appropriate.

Data analysis

Summary and scale scores were calculated for parent proxies and children (age ≥ 5 years).[5] Descriptive statistics were summarized by means and standard deviations for continuous variables and percent and numbers for categorical variables. Chi-square and Wilcoxon tests were done to compare categorical and continuous variables respectively. Comparison of HRQL between hydroxyurea and no hydroxyurea groups was done using linear regression analysis adjusting for age, gender, genotype and disease severity due to the potential impact these variables may have on HRQL. The Minimal Important Difference for the PedsQL Generic core scales summary scores is 4.4.[2] Analysis and figures were performed with R: A language for data analysis and graphics.[24] For the purposes of reporting, a p-value of 0.05 was considered statistically significant.

RESULTS

One hundred ninety-one children with SCD (mean age 10.4±4.7 years; 51% male; 99% Black/African American) and their caregivers were included in the study (Table 1). At the time of HRQL assessment 114 children had been taking hydroxyurea for 48.7 ± 31.4 months. Reasons for starting hydroxyurea included recurrent vaso-occlusive pain, recurrent or single episode of life threatening ACS, primary or secondary stroke prevention, and/or participation in a clinical research trial. No children were participating in a clinical trial at the time of this study. Compared to children in the no hydroxyurea group (n=77), children in the hydroxyurea group were older ($p<0.001$) and more had the SS genotype ($p<0.001$) and a history of severe disease ($p<0.001$), including 7 with a history of stroke.

The Parent Proxy Report was completed by the mother (159/191), father (16/191), or other legal guardian (16/190). Table 2 shows the median (IQR) subscale and composite scores for parent proxies and children.

Differences in HRQL in children receiving hydroxyurea therapy versus those not receiving HDU therapy

After adjusting for age and disease severity, children in the hydroxyurea group had higher median [IQR] PedsQL self-report total scale scores than children in the no hydroxyurea group (hydroxyurea group 75 [62.0, 86.4], no hydroxyurea group 69.0 [54.1, 79.9]; p=0.04). Child self-report physical functioning scores were significantly higher for children taking hydroxyurea (hydroxyurea group 79.7 [62.5, 90.6], no hydroxyurea group 71.4 [58.6, 81.2]; p=0.01). Similarly, parent proxy-report physical functioning scores were significantly higher for children taking hydroxyurea (hydroxyurea group 75 [53.9, 87.5], no hydroxyurea group 71.9 [53.2, 90.6]; p =0.05).

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DISCUSSION

Children with SCD who are taking hydroxyurea therapy report better physical functioning and overall HRQL than those not taking the medication despite disease severity and older age. This study provides important information on the impact of a disease modifying therapy, hydroxyurea, on the HRQL of children with SCD. It is well known that hydroxyurea therapy decreases the frequency of vaso-occlusive episodes but the effect this medication has on patient-reported outcomes in children with SCD has not been previously described.

Investigators have previously found that physical functioning scores correlate with current disease severity in children with SCD.[3] Our results demonstrate that children taking hydroxyurea have less severe current disease state and improved HRQL. Although hydroxyurea requires a commitment to take daily medication and attend more clinic visits for frequent monitoring, total and physical health scores were likely improved due to the impact we know hydroxyurea has on painful events.[9,12,25] In addition to reducing acute painful events, hydroxyurea may be associated with fewer self-reported problems with low energy and physical activities such as participating in active play and exercise as measured by the physical health domain.

It was not surprising that we found no differences between groups in the psychosocial summary score or its individual domains. Further research is needed to determine how to modify the emotional and social impact of SCD. Despite clinical response to hydroxyurea, children with SCD may experience decreased emotional and social well being since they still deal with a chronic disease on a daily basis. In addition, we did not see differences in school functioning between the two groups. This may be related to the fact that neurocognitive changes start early in life.[26,27] and hydroxyurea may need to be started at a very young age to decrease neurocognitive deficits associated with SCD[11]. In addition, school performance and academic attainment are influenced by multiple issues such as socioeconomic status and environment.

Limitations

A significant limitation of the study is the retrospective design. A prospective study of hydroxyurea may allow for pre- and post-comparisons of HRQL in children who are placed on hydroxyurea therapy and help delineate changes in HRQL over time in those children taking hydroxyurea compared to those who are untreated. However, given the ethical issues involved in withholding hydroxyurea from a child who has severe SCD, a randomized, placebo controlled trial is not feasible. Thus, although retrospective in design, our study provides a unique opportunity to determine differences in HRQL in children receiving and not receiving hydroxyurea. We did not include hematologic parameters or rates of pain in the data analyses. Therefore, we do not know whether laboratory markers of hydroxyurea or clinical response correlate with improvements in HRQL. Conclusions may be biased by characteristics of patients who participated in the study since children who come to clinic more frequently were more likely to have a chance to participate in the study. We have not studied differences in HRQL between patients who attend clinic regularly and those who do not. The study is also restricted by a lack of disease specific HRQL instrument. Although investigators have shown the validity and reliability of the PedsQL in children with SCD,[28,29] disease specific instruments are under development and should improve HRQL assessment for SCD by focusing on facets of SCD that are not assessed in generic instruments and improving the ability to detect changes within the population of patients with SCD.[2,30] Lastly, the study is a two-institution study, and individual center practices may affect the generalizability of the study.

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In conclusion, although children with SCD taking hydroxyurea were older and had a history of more severe disease, they had significantly better HRQL than children not taking hydroxyurea, particularly in the physical health domain. These findings provide a quantifiable measure of the differences in well being, from the *patient's perspective*, between children receiving or not receiving hydroxyurea therapy. Given these findings, perhaps using impaired HRQL as an additional indication to administer hydroxyurea to children with SCD is plausible. Further study of HRQL as an outcome in future hydroxyurea research and in clinical practice to measure the effectiveness of hydroxyurea for individual children will help our understanding of the full impact hydroxyurea has on the lives of children with SCD.

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REFERENCES

1. Bonner MJ. Health related quality of life in sickle cell disease: just scratching the surface. Pediatr Blood Cancer. 2010; 54(1):1–2. [PubMed: 19785024]
2. Panepinto JA. Health-related quality of life in sickle cell disease. Pediatr Blood Cancer. 2008; 51(1): 5–9. [PubMed: 18338399]
3. Panepinto JA, O'Mahar KM, DeBaun MR, et al. Health-related quality of life in children with sickle cell disease: child and parent perception. Br J Haematol. 2005; 130(3):437–444. [PubMed: 16042695]
4. Palermo TM, Schwartz L, Drotar D, et al. Parental report of health-related quality of life in children with sickle cell disease. J Behav Med. 2002; 25(3):269–283. [PubMed: 12055777]
5. Ingerski LM, Modi AC, Hood KK, et al. Health-related quality of life across pediatric chronic conditions. J Pediatr. 2010; 156(4):639–644. [PubMed: 20117793]
6. Brandow AM, Brousseau DC, Pajewski NM, et al. Vaso-occlusive painful events in sickle cell disease: impact on child well-being. Pediatr Blood Cancer. 2010; 54(1):92–97. [PubMed: 19653296]
7. Zimmerman SA, Schultz WH, Davis JS, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood. 2004; 103(6): 2039–2045. [PubMed: 14630791]
8. Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood. 2005; 106(7):2269–2275. [PubMed: 16172253]
9. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. Pediatrics. 2008; 122(6):1332–1342. [PubMed: 19047254]
10. Ballas SK, Barton FB, Waclawiw MA, et al. Hydroxyurea and sickle cell anemia: effect on quality of life. Health Qual Life Outcomes. 2006; 4:59. [PubMed: 16942629]
11. Thornburg CD, Dixon N, Burgett S, et al. A pilot study of hydroxyurea to prevent chronic organ damage in young children with sickle cell anemia. Pediatr Blood Cancer. 2009; 52(5):609–615. [PubMed: 19061213]
12. Charache S, Terrin ML, Moore RD, et al. 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(20):1317–1322. [PubMed: 7715639]
13. Panepinto JA, O'Mahar KM, DeBaun MR, et al. Validity of the child health questionnaire for use in children with sickle cell disease. J Pediatr Hematol Oncol. 2004; 26(9):574–578. [PubMed: 15342984]

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14. Scott JP, Hillery CA, Brown ER, et al. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr. 1996; 128(6):820–828. [PubMed: 8648542]
15. Varni J. The PedsQL™ 4.0 Measurement Model for the Pediatric Quality of Life Inventory™ Version 4.0: Administration Guidelines. 2004 http://wwwpedsqlorg/pedsqladminhtml <http://www.pedsql.org/pedsqladmin.html>.
16. Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population health measure: feasibility, reliability, and validity. Qual Life Res. 2006; 15(2):203–215. [PubMed: 16468077]
17. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003; 3(6):329–341. [PubMed: 14616041]
18. Varni JW, Burwinkle TM, Jacobs JR, et al. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. Diabetes Care. 2003; 26(3):631–637. [PubMed: 12610013]
19. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer. 2002; 94(7):2090–2106. [PubMed: 11932914]
20. Varni JW, Burwinkle TM, Rapoff MA, et al. The PedsQL in pediatric asthma: reliability and validity of the Pediatric Quality of Life Inventory generic core scales and asthma module. J Behav Med. 2004; 27(3):297–318. [PubMed: 15259457]
21. Varni JW, Seid M, Smith Knight T, et al. The PedsQL in pediatric rheumatology: reliability, validity, and responsiveness of the Pediatric Quality of Life Inventory Generic Core Scales and Rheumatology Module. Arthritis Rheum. 2002; 46(3):714–725. [PubMed: 11920407]
22. Panepinto JA, Pajewski NM, Foerster LM, et al. The performance of the PedsQL generic core scales in children with sickle cell disease. J Pediatr Hematol Oncol. 2008; 30(9):666–673. [PubMed: 18776758]
23. Dampier C, Lieff S, LeBeau P, et al. Health-related quality of life in children with sickle cell disease: a report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. Pediatr Blood Cancer. 2010; 55(3):485–494. [PubMed: 20658620]
24. RDC Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2004. Available at: http://www.R-project.org. [Accessed: August 31, 2010]
25. Stallworth JR, Jerrell JM, Tripathi A. Cost-effectiveness of hydroxyurea in reducing the frequency of pain episodes and hospitalization in pediatric sickle cell disease. Am J Hematol. 2010
26. Wang WC, Langston JW, Steen RG, et al. Abnormalities of the central nervous system in very young children with sickle cell anemia. J Pediatr. 1998; 132(6):994–998. [PubMed: 9627592]
27. Wang WC, Pavlakis SG, Helton KJ, et al. MRI abnormalities of the brain in one-year-old children with sickle cell anemia. Pediatr Blood Cancer. 2008; 51(5):643–646. [PubMed: 18478575]
28. Panepinto JA, Foerster LM. Disease severity in sickle cell disease: understanding impairment in health-related quality of life. Blood. 2007; 110(11):957a.
29. McClellan CB, Schatz J, Sanchez C, et al. Validity of the Pediatric Quality of Life Inventory for Youth with Sickle Cell Disease. J Pediatr Psychol. 2008; 33(10):1153–1162. [PubMed: 18400838]
30. Marino BS, Shera D, Wernovsky G, et al. The development of the pediatric cardiac quality of life inventory: a quality of life measure for children and adolescents with heart disease. Qual Life Res. 2008; 17(4):613–626. [PubMed: 18347927]

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TABLE 1

Demographics and Disease Characteristics of Study Cohort (N=191)

	Overall	Hydroxyurea	No Hydroxyurea	p-value
N	191	114	77	NA
Mean Age, years	10.4±4.7	11.4±4.2	9.0±5.1	p<0.001
Gender, N (%)				
Female	93 (48.7)	54 (47.4)	39 (50.6)	p=0.66
Genotype, N (%)				
SCD-SS	141 (73.8)	102 (89.5)	39 (50.6)	p<0.001
SCD-SC	34 (17.8)	7 (6.1)	27 (35.1)	
SCD-S beta^{+} thalassemia	10 (5.2)	1 (0.9)	9 (11.7)	
SCD-S beta^{0} thalassemia	4 (2.1)	3 (2.6)	1 (1.3)	
SCD-S OArab	1 (0.5)	1 (0.9)	0	
SCD-S GPhiladelphia	1 (0.5)	0	1 (1.3)	
Disease Severity*, N (%)				
Severe	103 (54.2)	75 (66.4)	28 (36.4)	p<0.001
Duration of hydroxyurea therapy, months	-	49±31	-	-

*Severe disease was defined as a history stroke, acute chest syndrome, and/or 3 or more hospitalizations for vaso-occlusive pain in the prior three years.

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TABLE 2

Health related quality of life for children with sickle cell disease

	Hydroxyurea Median (IQR)	No Hydroxyurea Median (IQR)	p-value*
Child			
Total	75 (62.0,86.4)	69.0 (54.1	0.04
Physical health	79.7 (62.5,90.6)	71.4 (58.6	0.01
Psychosocial health	73.3 (60.0, 86.7)	68.3 (50.0	0.16
Emotional functioning	75.0 (60.0, 90.0)	68.3 (53.8	0.07
Social functioning	80.0 (65.0, 96.2)	80.0 (60.0	0.46
School functioning	70.0 (50.0, 80.0)	60.0 (47.5	0.12
Parent-proxy			
Total	71.7 (51.1,86.9)	70.7 (56.8,83.6)	0.10
Physical health	75 (53.9,87.5)	71.9 (53.2,90.6)	0.05
Psychosocial health	71.7 (53.3, 86.7)	69.5 (57.1, 83.3).	0.18
Emotional functioning	75.0 (56.2, 90.0)	75.0 (63.1, 90.0)	0.39
Social functioning	75.0 (55.0, 95.0)	75.0 (63.1, 93.8)	0.22
School functioning	60.0 (41.3, 80.0)	55.0 (45.0, 73.8)	0.16

*adjusted for age, gender, genotype and disease severity