Treatment adherence and quality of life outcomes in patients with sickle cell disease

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ABSTRACT

الأهداف: تقييم جودة الحياة للمرضى المصابين بفقر الدم المنجلي وقياس دور الالتزام بالعلاج في تطور أعراض المرض، شدته وأزمته ونتائجه.

الطريقة: أجريت دراسة مقطعية على المرضى الذين يراجعون عيادة أمراض الدم، مستشفى جامعة الملك عبدالعزيز خلال الفترة من يناير 2009م إلى ديسمبر 2011م. قمنا بقياس نتائج مقياس جودة الحياة باستخدام آداة مقياس جودة الحياة لمنظمة الصحة. تم جمع البيانات وتحليلها باستخدام حزمة البرنامج الإحصائي للعلوم الإجتماعية ثم تحليل نتائج الدراسة.

النتائج: أكمل 115 مريض الاستبيان. ووجدنا 87 (75.7%) لديهم أعراض شديدة لفقر الدم المنجلي، بينما 28 (24.3%) لديهم أعراض بسيطة. ارتبطت جودة حياة المرضى المصابين بفقر الدم المنجلي بشدة أعراض المرض p=0.002 . أظهرت الدراسة أن أزمات الألم كذلك من الأسباب المؤدية للتنويم 51.3% ;n=59. كما استخدم 36 مريضاً 31.3% يعانون من أزمات الألم المهدئات وكانت درجات جودة الحياة لديهم متدنية p=0.0001. كلما ازدادت درجات الألم كلما انخفضت درجات جودة الحياة. أظهرت النتائج كذلك بأن المرضى الذين لم يلتزموا وتأخروا في العلاج كانت درجات جودة الحياة لديهم متدنية p=0.001.

خاتمة: أن الالتزام بالعلاج والعلاج المبكر للمرضى المصابين بفقر الدم يحسن من جودة الحياة لديهم.

Objectives: To assess the health-related quality of life (HRQL) of patients with sickle cell disease (SCD) and to measure the impact of treatment adherence on disease complication, severity, crisis, and outcome.

Methods: This was a cross-sectional study on patients with SCD who attended the Hematology Clinic at King Abdulaziz University Hospital from January 2009 to December 2011. We measured the primary outcome of health-related quality of life (HRQL) using the World Health Organization quality of life assessment instrument (WHOQOL-BREF). Data were collected and analyzed using the Statistical Package for Social Sciences. Analysis of HRQL was carried out along the scoring of WHOQOL-BREF.

Results: One hundred fifteen patients completed the questionnaire. Eighty-seven patients (75.7%) had severe SCD, while 28 (24.3%) had mild disease. Patients with severe disease had a low HRQL (p=0.002). Pain episodes were the main cause of hospitalization (n=59; 51.3%). Thirty-six of patients (31.3%) who had pain episodes were on regular narcotics and had low HRQL scores (p=0.0001). The HRQL scores significantly decreased as pain levels increased. Patients with delayed treatment or those who were not adherent to treatment showed worse HRQL scores (p=0.001).

Conclusions: Treatment adherence and early intervention in SCD improved HRQL outcomes.

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The natural history of sickle cell disease (SCD) is highly variable, with clinical manifestations ranging from acute life-threatening infections to chronic sequelae, and organ damage, such as chronic neuropsychological and locomotor disabilities. However, in assessing the seriousness of SCD, the emotional and social impacts are often underestimated. Traditional methods of measuring the impact of SCD involve determining the morbidity and mortality related to its common complications.[1] The measurement of health-related quality of life (HRQL) in patients with SCD is an

alternative method to assess the impact of the disease on patients and their families. Health-related quality of life is commonly defined as the patient's physical, emotional, and social well-being. When assessing the emotional, physical and social effects of treatments and disease processes on people's daily lives, quality of life analyses are particularly useful. Quality of life is deteriorated by episodes of debilitating pain associated with substantial analgesic use, frequent hospitalization for pain, disease complication, and ultimately organ failure. Recently, the patient health questionnaire (PHQ) was validated for use in children and adults with SCD, and it was shown to be very reliable.[2-7] In this study, we assess HRQL of patients with SCD and measure the impact of treatment adherence on disease severity, complications, and outcome using the World Health Organization quality of life assessment instrument (WHOQOL-BREF).[8] In previous studies, the WHOQOL-BREF has shown good to excellent reliability and validity, with good psychometric properties in determining the quality of life in patients with SCD.[9,10] It is crucial to examine HRQL in patients of different age groups. In Saudi Arabia, few studies have been conducted to assess HRQL in patients with SCD. The most recent study that was conducted in 2011 assessed HRQL in a sample of Saudi Arabian adolescents with SCD. The authors reported a significant deterioration of HRQL (physical, general health, and emotional) in adolescents with SCD.[11]

Methods.

Study settings and subjects. This cross-sectional study was conducted in patients with SCD who were followed up at the Hematology Clinic, King Abdulaziz University Hospital (KAUH) between January 2009 and December 2011. King Abdulaziz University Hospital is a tertiary medical center in Jeddah, western region of Kingdom of Saudi Arabia. We included all patients with SCD who presented to the hematology clinic for routine visit. Patients were excluded from the study if they refused to filled up the questionnaire. Consent was obtained from all patients prior to inclusion criteria. Permission to conduct the study was obtained from the Ethics Research Committee of King Abdulaziz University.

Data collection. The primary outcome of HRQL was measured using the WHOQOL-BREF. The WHOQOL-BREF is structured as domains and facets, it consists of 26 questions, namely 2 general on the quality of life and 24 corresponding to each of the facets of the original instrument. These were divided into 3 domains: physical health (7 items), psychological health (6 items), and social relationships (3 items). The form was self-filled by adult patients, and in the case of children, by their parents. We recorded the age, gender, level of education, marital status, and income of the patients. Additional data was obtained by reviewing the medical records of the patients. We also recorded the hemoglobinopathy type, disease status, and documented medical comorbidities.

The patient's disease status was classified as mild or severe regardless of his or her sickle cell phenotype. The following disorders or disease complications were considered as severe if the patient had a history of stroke, acute chest syndrome, more than 3 hospitalizations for vaso-occlusive crises (VOC) in the prior 3 years, bone complications (for example, aseptic necrosis, osteoporosis or osteomyelitis), recurrent priapism, or any disease complication which required frequent admission. Patients were also classified to have severe disease when they had a history of long-term blood transfusions or had received hydroxyurea. All others were classified to have mild disease. Patients were classified to have neurobehavioral comorbidities when one or more of the following conditions were present: anxiety problems, attention problems, behavioral problems, depression, developmental delay or mental retardation, sleep disturbances, learning problems, seizures or speech problems. We also assessed patient's self-esteem, happiness, and satisfaction. Patients' treatments were analyzed for routine opioid or non-opioid use, and patient's treatment adherence was assessed through attendance to the clinic for follow-up.

Calculation of domain scores. The customized WHOQOL-BREF consists of 18 statements on negative consequences of health state, where every statement is rated on a 5-point Likert-type scale. Number 1 denotes poor adaptation to a disease and 5 its full acceptance. The score for acceptance is a sum of all points, and it can range from 8-40. Low scores (0-25) indicate unhappiness or lack of acceptance (unhappy). High scores (26-40) indicate happiness or lack of negative emotions associated with disease (happy). The 3 domains are represented in one summative figure correlated with different demographic and medical characteristics of the patients.

Data analysis. Descriptive statistics were calculated for all variables using the Statistical Package for the Social Sciences, version 18 (SPSS Inc., Chicago, IL,

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USA). Chi-square test was used to assess the association between SCD variables, education, neurobehavioral comorbidities, and HRQL. $P<0.05$ was considered statistically significant (with 95% confidence interval). The HRQL was analyzed along the scoring of WHOQOL-BREF in all domains.

Results. *Demographic characteristics.* We recruited 115 patients with SCD. Fifty-two (45.2%) were males and 63 (54.8%) were females. Patient's age ranged from 2-48 years (mean ± SD 19.80±8.8 years); 23 patients (20.01%) were aged 1-12 years, 33 (28.7%) were 13-18 years, and 59 (51.3%) were >18 years. Most of the patients (n=81; 70.5%) had a low income. Sixty-eight patients (59.2%) were educated, 21 patients (36%) were married and 38 (64%) were single.

Clinical characteristics of patients. Most patients (n=95; 85.6%) had the SS genotype; 17 (15.7%) had SB^0 genotype, while 2 patients (1.7%) had SB^+ genotype. Eighty-seven patients (75.7%) had severe SCD, while 28 (24.3%) had mild disease. Pain episodes were the main cause of hospitalization, documented in 59 patients (51.3%). Sixteen patients (13.9%) had radiologically-verified multiple osteonecrosis, age range from 11-22 years. Avascular necrosis of both femoral heads occurred in 10 patients; avascular necrosis of the femoral and humeral head occurred in 5 patients, and in one patient both humeral heads were affected. Symptomatic osteonecrosis was reported in all 16 patients, 15 out of 16 were on regular opioids for pain. There was a high prevalence of vitamin D3 deficiency, with 63 (54.8%) cases of severe deficiency (levels ≤25nmol/L; reference range, 50-80 nmol/L). Twenty-two patients (19.2%) had osteoporosis based on abnormal bone mineral density (BMD). Twenty-two patients (19.2%) had a stroke. Their age ranged from 1-24 years. Ten patients (8.7%) had a recurrent serious infection. Complications involving the spleen were documented in 12 cases (10.4%). Thrombosis, acute chest syndrome, and delayed puberty/short stature were observed in 5 patients (4.3%) each. Priapism was reported in 2 patients (1.7%), and the youngest patient presented at the age of 6 years.

Health-related quality of life of patients. The association between sickle cell variables and HRQL are shown in **Table 1**. There were no significant differences in the demographic data, including marital status, and income. However, significant differences were observed between educated (63% happy) and non-educated patients (37% unhappy) (p=0.01). There were significant differences among various age groups as young patients were happier than the elderly (74% versus 42% for the elderly) (p=0.024). A significant trend was found between complicated clinical conditions (p=0.001 in all cases) mainly in patients with chronic pain (73% unhappy), patients on regular narcotics (75% unhappy), patients suffering from aseptic necrosis (94% unhappy) p=0.0001, and neurobehavioral comorbidities (66% unhappy) p=0.001. There was significant difference between the number of happy to unhappy patients regarding patient compliance and treatment adherence (76% versus 24% of unhappy patients, p=0.001). There were no significant differences between happy

Table 1 - Health-related quality of life in patients with sickle cell disease (N=115).

Variable	HRQL		Total	Pearson Chi-square	*P*-value
	Unhappy	Happy			
Age group (years)				7.460	0.024
1-12	6	17	**23**		
13-18	13	20	**33**		
>18	34	25	**59**		
Marital status				1.701	0.192
Married	9	12	**21**		
Single	23	15	**38**		
Income				0.468	0.494
Low	39	42	**81**		
High	14	20	**34**		
Education				6.691	0.01
Yes	25	43	**68**		
No	11	4	**15**		
Disease complications				9.592	0.002
Mild	4	24	**28**		
Severe	41	46	**87**		
CVA				1.851	0.174
Yes	13	9	**22**		
No	40	53	**93**		
Infection				0.067	0.795
Yes	5	5	**10**		
No	48	57	**105**		
Bone mineral density				0.004	0.947
Normal	43	50	**93**		
Abnormal	10	12	**22**		
Vitamin D status				0.635	0.728
Normal	4	6	**10**		
Deficient	20	19	**39**		
Severe deficiency	28	35	**63**		
Pain episodes				35.009	0.0001
Yes	43	16	**59**		
No	10	46	**56**		
Aseptic necrosis				17.384	0.0001
Yes	15	1	**16**		
No	37	61	**98**		
Narcotic use				17.631	0.0001
Yes	27	9	**36**		
No	26	53	**79**		
Neurobehavioral co-morbidity				21.806	0.001
Yes	35	18	**53**		
No	6	31	**37**		
Treatment adherence				28.906	0.001
Yes	14	45	**59**		
No	27	6	**33**		

Data are presented as frequency unless otherwise stated.
CVA - cerebrovascular accident, HRQL - health-related quality of life.

and unhappy patients regarding vitamin D3 deficiency, stroke, abnormal bone mineral density, and recurrent serious infections.

Discussion. The quality of life of patients with SCD is deteriorated by episodic, debilitating pain associated with frequent hospitalization for disease complications. In this study, we assess whether comprehensive medical treatment is effective to improve the HRQL in patients with SCD. Recent studies conducted in the western region of Saudi Arabia have shown that patients with SCD have a severe, non-benign course compared to those in the eastern region.[12-14] In this study, 76% of patients had severe disease. The HRQL was significantly reduced in patients with severe SCD-related complications compared to those who had mild complications. However, nearly half of the patients with severe disease complications reported they were happy. It is plausible that these patients, despite having severe disease, had higher self-esteem and were happy because of other factors, such as education, faith, absence of neurobehavioral problems, social competence, and adherence to treatment. Pain episodes are frequent in patients with SCD.[15-17] Opioids are routinely used in the management of acute pain crises in patients with SCD.[17] Approximately half of our patients were frequently hospitalized due to pain episodes, which explains the significantly lower HRQL score in patients who had pain crises. Patients on regular narcotics showed low scores in all domains due to uncontrolled pain episodes. Aseptic necrosis, a devastating clinical complications with chronic progressive disability, was frequent in our patients. Currently, early intervention by surgical replacement of the femoral or humeral head is highly recommended for the treatment of early avascular necrosis.[18,19] Fifteen of 16 patients with multiple osteonecrosis were on regular narcotics due to delayed medical intervention. Hydroxyurea had no effect in alleviating pain or stopping the progression of osteonecrosis in our patients. Hydroxyurea has been reported to be effective in pain control and some disease complications with SCD.[2,20,21] Studies have shown an increased risk of vitamin D3 deficiency in patients with SCD.[20,22,23] In the current study, severe vitamin D3 deficiency was diagnosed in 63 patients (54.7%), and 21 of these patients were on regular narcotics because they were not adherent to medical treatment. We showed that there was a significant difference between the proportion of happy to unhappy patients regarding patient compliance and treatment adherence (76% versus 24% of unhappy patients). According to previous reports, adherence to comprehensive care by a multi-disciplinary team and preventive measures minimize the mortality, morbidity and improve quality of life in SCD.[1,4,6,20,24]

Study limitations. Our analysis of neurobehavioral comorbidities was limited by the self-reporting nature of the questionnaire. Considerable knowledge has been gained regarding the SCD. However, we showed that the risk of developing disease complications was increased at a younger age. Clarifying the clinical course has enabled us to develop therapies, or early interventions in treatment or prevention to decrease the morbidity of this disease.

In conclusion, early medical intervention and adherence to treatment improve the quality of life in SCD. HRQL measures should be applied in all centers treating patients with SCD.

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