Erciyes Med J 2021; 43(3): 273–7 • DOI: 10.14744/etd.2020.06337
ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of the Effect of Mortality, Life Expectancy, and Treatment Modalities of Sickle Cell Patients on Mortality

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ABSTRACT

Objective: We aimed to contribute to the literature by investigating the causes of mortality, average life expectancies, and the clinical features that occur in this process, in relation to sickle cell disease (SCD), and by comparing the results obtained with other similar clinical studies.

Materials and Methods: This study was designed as a monocentric, cross–sectional, and retrospective study. The patient files were reviewed in terms of the age, use of hydroxyurea, use of chelators, exchange transfusion history, surgical operation history, the annual frequency of painful crises, the annual hospitalization frequency, and the annual frequency of follow–up visits which the patients have attended, the complications experienced by the patients, and the causes of mortality.

Results: Acute chest syndrome was the most prevalent cause of death of the patients included in our study. No significant difference was found between the premature death and late death groups, that is, the groups that we have determined on the basis of the SCD patients ages of death, in terms of use of hydroxyurea, use of iron chelator, and use of exchange transfusion depending on the disease.

Conclusion: Based on our findings, acute chest syndrome was the primary cause of death in SCD patients we have studied, followed by pulmonary embolism. Use of hydroxyurea, use of iron chelator, exchange transfusion history, and surgical operation history due to SCD were not found to be significantly effective when the mean age of death reported in the literature was taken as the base value.

Keywords: Hydroxyurea, mortality, sickle cell disease

Cite this article as:
Kaya MN, İlhan G. Evaluation of the Effect of Mortality, Life Expectancy, and Treatment Modalities of Sickle Cell Patients on Mortality. Erciyes Med J 2021; 43(3): 273-7.

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Submitted
26.05.2020

Accepted
02.12.2020

Available Online
19.04.2021

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INTRODUCTION

Sickle cell disease (SCD) is a heterogeneous hereditary type of blood disease that exhibits an autosomal recessive transition which develops as a result of the damaged synthesis of hemoglobin (Hgb) protein, which is the molecule that carries oxygen to tissues. Mutant Hgb S is the most common and clinically relevant Hgb structural variant worldwide, but there are no precise data on its frequency in affected populations (1). Among the common comorbid diseases of the SCD are chronic hemolysis, anemia, typical painful crises, and tissue as well as organ damage, and its clinical course varies widely. It is geographically widely prevalent encompassing Africa, the Middle East, the Americas, India, and the Mediterranean coastal regions, which also includes our country (2). In Africa, the mortality rate of children with SCD has been determined to be high, with 50–90% of the patients dying early in childhood; in other words, approximately 1000 babies are born with SCD every day in Africa, and more than half of them die before they reach 5 years old. Childhood mortality rates have decreased significantly in underdeveloped and developing countries due to the fact that the SCD can now be diagnosed early (3). SCD is most commonly seen in the Mediterranean region in Turkey, and it was determined that 13.6% of the population living in the said region have the disease (2). SCD leads to a significantly lower life expectancy as it is a progressive disease that can lead to life–threatening irreversible organ damage (4). Three main therapeutic options are used in SCD: Hydroxyurea, exchange transfusion, and stem cell transplantation. There are a few studies where the factors that affect the mortality in SCD patients were researched, however, the effect of hydroxyurea on the mortality rates of adult patients is not pronounced (5). On the other hand, the use of stem cell transplantation offers a limited therapeutic option, since it can only be performed in a limited number of centers. These therapies and enhancements may prolong survival time by treating acute complications. As chronic complications may develop without presenting any symptoms, patients should be monitored regularly by the clinician and the treatment team as part of a health–care program (6). In a study conducted on children with SCD, screening, and preventive measures, including vaccination and infection prophylaxis, were found to increase survival (7). Variables in respect of SCD, such as the causes of death, ages of death, and mortality rates, have been widely researched over the years, with the exception of the clinical features of SCD. Such studies are important in terms of the contributions they make to the improvement of the therapeutic options and the development of medical care

services offered to patients. In this study, we aimed to contribute to the literature by investigating the causes of mortality, average life expectancies, and the clinical features that occur in the disease progression in relation to SCD, as well as comparing the results obtained with other similar clinical studies.

MATERIALS and METHODS

Study Design and Sampling

Our hospital where the study was conducted is located in the Eastern Mediterranean Region of Turkey. The region's highest number of SCD patients is followed in our hospital. Our study was conducted at the hematology clinic of our university in the faculty of medicine. This study was designed as a single–center, cross–sectional, and retrospective study. Patients that have died due to SCD from among the patients who were followed up in our hospital's hematology clinic between the years of 2005 and 2020 comprised the study sample. Mustafa Kemal University Ethics Committee approved the present study in accordance with the Declaration of Helsinki (Date of Approval: June 04, 2020; Reference number/ Protocol No: 20).

Inclusion criteria were SCD cases available in the hospital data system based on the definition as per the International Classification of Diseases (ICD). The relevant ICD codes (ICD–10 [ICD 10th Revision]) are as follows; D57.0, sickle cell anemia with crisis; D57.1, sickle cell anemia without crisis; D57.2, double heterozygous SCDs; D57.8, other sickle cell disorders; D56.8, and sickle cell beta–thalassemia (8). Patients without SCD and patients younger than 16 years were excluded from the study. The patient files were reviewed in terms of the age, use of hydroxyurea, use of chelators, exchange transfusion history, surgical operation history, the annual frequency of painful crises, the annual hospitalization frequency, the annual frequency of follow–up visits which the patients have attended, the complications experienced by the patients, and the causes of mortality. In the meta–analysis study conducted by Maitra et al. (9), with regard to SCD mortality rates in North America and Europe, the average age of death due to SCD was found to be 50 years. We predicated "50 years," the average age of death due to SCD reported in the said meta–analysis study, as the average life span of the patients included in our study. One reason for choosing this study was that the said meta–analysis study was carried out fairly recently and had involved a significant number of patients. Therefore, we have defined deaths due to SCD that has occurred before the age of 50 as premature deaths and the deaths due to SCD that has occurred after the age of 50 as late deaths to determine the effect of SCD–related use of hydroxyurea, use of chelators, exchange transfusion history, and surgical operation history, on the average life span of the patients.

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) 23.0 (SPSS Inc., Chicago, IL, USA). Categorical measurements are expressed as the number and percent, and continuous variables as the mean±standard deviation or median and minimum–maximum when required. Categorical variables were compared using the Chi–square test. The Mann–Whitney U–test is used to compare the differences in survival times of groups according to the use of hydroxyurea, use of iron chelator, exchange transfusion history, and surgical operation history. P<0.05 was considered to indicate statistical significance.

Table 1. Certain sociodemographic characteristics and clinical features of patients

Certain sociodemographic characteristics	
Gender, n (%)	
Male	23 (35.9)
Female	41 (64.1)
Age (median, minimum–maximum)	42.5 (20–85)
Hospitalization frequency (yearly)	2.2±0.8
Frequency of follow–up visits patients has attended (yearly)	1.1±0.7
Frequency of painful crisis (yearly)	1.3±0.7
Complications, n (%)	
Autosplenectomy	32 (50)
Cholelithiasis	23 (35.9)
Acute chest syndrome	12 (18.7)
Splenic sequestration crisis	10 (15.6)
Pulmonary hypertension	9 (14)
Deep vein thrombosis	4 (6.2)
Cerebrovascular obstruction	2 (3.1)

RESULTS

Sixty–four patients that were being followed up in our clinic and who died of SCD were included in this study. Twenty–three (35.9%) of the cases were male and 41 (64.1%) were female. The median age of the patients was 42.5 (20–85) years, whereas the median age of the female and male patients was 49 (26–68) and 41 (20–85) years, respectively. Among the patients included in the study, the patient with the lowest age was 20 years old and the patient with the highest age was 85 years old. The average annual hospitalization frequency of the patients was 2.2±0.8, the average annual frequency of follow–up visits, which the patients have attended, was 1.1±0.7, and the average annual frequency of the painful crisis of the patients was 1.3±0.7. The most common complication associated with SCD was autosplenectomy, which was seen in 50% of the cases. Other common complications were cholelithiasis, acute chest syndrome, splenic sequestration crisis, and pulmonary hypertension, other complications being were less common (Table 1). Sickle cell patients can die for many reasons at an early age compared to the healthy population depending on the underlying disease. Acute chest syndrome was the most prevalent cause of death of the patients included in our study. Other causes are pulmonary embolism, sepsis, chronic renal failure, congestive heart failure, painful crisis and multiorgan failure, liver cirrhosis, splenic sequestration, and other rare causes, respectively, followed acute chest syndrome in this regard (Table 2). No significant difference was found between the premature death and late death groups, that is, the groups that we have determined on the basis of the SCD patients ages of death, in terms of use of hydroxyurea, use of iron chelator, use of exchange transfusion, and frequency of the surgical operations depending on the disease (p>0.05) (Tables 3, 4).

Table 2. Causes of deaths

Cause	n	%
Acute chest syndrome	8	12.5
Pulmonary embolism	7	10.9
Sepsis	6	9.3
Chronic renal failure	6	9.3
Congestive heart failure	5	7.8
Painful crisis and multiorgan failure	4	6.2
Liver cirrhosis	4	6.2
Splenic sequestration	4	6.2
Acute renal failure	3	4.6
Pulmonary edema	2	3.1
Chronic obstructive pulmonary disease	2	3.1
Acute respiratory distress syndrome	2	3.1
Pulmonary hypertension	1	1.5
Subarachnoid bleeding	1	1.5
Esophageal variceal bleeding	1	1.5
Chronic myeloid leukemia	1	1.5
Myelofibrosis	1	1.5
Myocardial infarction	1	1.5
Post–operative	1	1.5
Gallbladder perforation	1	1.5
Unidentified	3	4.6
Total	64	100

Table 3. Relationship between age of death and clinical features

Variables (n)	Age			
	Mean	U	Z	p*
Use of hydroxyurea				
Yes (35)	31.9	489.50	-0.24	0.80
No (29)	33.1			
Use of iron chelator				
Yes (14)	38.1	271.00	-1.28	0.19
No (50)	30.9			
Use of exchange transfusion				
Yes (13)	26.1	249.50	-1.36	0.17
No (51)	34.1			
Surgical operation history				
Yes (19)	32.3	425.00	-0.03	0.97
No (45)	32.5			

*: Mann–Whitney U–test

Table 4. Comparison of groups according to clinical features

Variables	Premature death		Late death		p**
	n	%*	n	%*	
Use of hydroxyurea					
Yes	26	74.3	9	25.7	0.44
No	19	65.5	10	34.5	
Use of iron chelator					
Yes	10	71.4	4	28.6	0.91
No	35	70	15	30	
Use of exchange transfusion					
Yes	9	69.2	4	30.8	0.92
No	36	70.6	15	29.4	
Surgical operation history					
Yes	12	63.2	7	36.8	0.41
No	45	73.3	12	26.7	

*: Percentage in respect of the respective row; **: Chi–square test

DISCUSSION

Hamideh and Alvarez reported the respiratory system as the second most frequently affected system that leads to death in patients with SCD. According to the same study, the most common cause of death among cardiovascular system–related causes was found to be pneumonia (8). Karacaoğlu et al. (10) reported acute chest syndrome as the most common cause of death in patients with SCD. According to this study, acute chest syndrome constituted the cause of death in 28.5% of patient deaths from SCD. Compared to the aforementioned studies, we have found acute chest syndrome as the most common cause of death in patients with SCD, just as Karacaoğlu et al. (10) did. In our study, acute chest syndrome constituted the cause of death in 12.5%. Pulmonary embolism, followed acute chest syndrome, was the second most common cause of death in patients with SCD in our study (Table 2). Maitra et al. (9) reported that 84% of the patients included in their study had acute chest syndrome and 15% of the patients died because of acute chest syndrome. In a study conducted in the United States in 1973, the average life span was reported to be 14.2 years for SCD patients (11). The average life expectancies of male and female patients with SCD that was followed up within the scope of a prospective study conducted in the Mediterranean Region of Turkey on 735 SCD patients, who had Hgb S variant Hgb, have been reported as 37 and 38 years, respectively (10). In comparison, the average life span of the SCD patients in North America and Europe was found to be 50.2 years in a meta–analysis study conducted by Maitra et al. (9). In our study, the average life span of SCD patients was found to be lower compared to other studies (Table 1). Among the factors that are considered to have an effect on this result are the genetic characteristics of the Mediterranean population where our hospital is located, the lack of better health services, nutrition problems, hygiene issues, low educational statuses, lack of vaccination, insufficient newborn screenings, low use of hydroxyurea, low use of prophylactic antibiotics to prevent infections and the problems that the older SCD patients face in accessing health services (12). SCD is characterized by chronic hemolysis, recurrent pain episodes (which are described as sickle cell–related pain crises or vaso–occlusive crises,

multiorgan dysfunction, and premature death). If these crises can be minimized, the risk of death of SCD patients can be minimized as well (13, 14). A bone marrow transplantation list has been declared by the Turkish Social Security Institution, who also define frequent painful crises as three or more painful attacks experienced a year, and rare painful crises as less than 3 painful attacks experienced a year (15). In a study conducted on 735 SCD patients in Turkey, 25% of patients had more than 3 painful crises (10). In a 10–year prospective study conducted by Hamideh and Alvarez in SCD patients in the USA, 20% of the 5416 patients who died due to SCD had a painful crisis (8). The average number of painful crises experienced per year was reported as 1.4 in the cohort study conducted by Freitas et al. (13) on patients with SCD. In our study, the average frequency of painful crises seen in patients was found to be 1.3 times a year, whereas the patient who had the most frequent painful crisis among our patients experienced three attacks a year (Table 1). The result of a multicenter hydroxyurea study indicated that the frequency of pain attacks decreased by 44% in patients with SCD after hydroxyurea treatment, initial pain episodes shortened, acute chest syndrome attacks lessened, and the need for exchange transfusion, as well as the frequency of hospitalization, decreased (16). Long–term follow–up revealed that the 10–year survival probability of SCD patients that received hydroxyurea treatment increased to 86% compared to the 10–year survival probability of SCD patients that did not receive the treatment, which is 65% (5). Hydroxyurea treatment in children with SCD was also researched and it has proven to be effective in reducing vaso–occlusive complications (17). A study conducted in Brazil on children with SCD revealed that the mortality rates in children with SCD that received hydroxyurea treatment were 4.6 times less than the mortality rates in children with SCD that did not hydroxyurea treatment. It was also stated in the same study that the rates of acute events such as hospitalization and transfusion were also decreased after treatment with hydroxyurea (18). However, it is also stated that hydroxyurea effect is not sufficient to prevent or treat specific organ damage, and more studies are needed in this regard (19). We have not found any statistically significant difference, in terms of premature and late deaths, between the SCD patients that received the hydroxyurea treatment and the SCD patients that did not (Table 3). There are only a few studies where it was reported that hydroxyurea reduces mortality, whereas, in our study, we have not found any significant difference between the median age of death and the use of hydroxyurea. The fact that our study involved a limited number of patients, and that there were non–SCD–related causes among the causes of death in our SCD patients, may have led to the difference between our findings and the findings reported in the few aforementioned studies. Exchange transfusion is a more effective method than erythrocyte transfusion in acutely reducing the rate of sickled Hgb in circulation. It is performed frequently in children with SCD who have had a stroke. It was determined that very first exchange transfusion in these children leads to a reduced risk of developing a second stroke. In other words, exchange transfusion may prevent recurrent stroke in pediatric patients with SCD (20). Many studies that favor the use of exchange transfusion in SCD patients also favor the use of exchange transfusion as pre–operative prophylaxis in the treatment of acute chest syndrome, multiorgan failure, SCD–related pregnancy, and in the treatment and prophylaxis of cerebrovascular complications (21). However, there are fewer studies on whether the use of exchange transfusion reduces mortality in SCD patients compared to the number of studies conducted on the effect of hydroxyurea on the mortality of SCD patients. Exchange transfusion in pregnant women with SCD has led to a statistically significant decrease in mortality compared to pregnant women with SCD who did not have an exchange transfusion (22). We have not found the effect of exchange transfusion on patients with SCD to be statistically significant, as have a number of other studies available in the literature (Table 3). It is clear, on the one hand, that exchange transfusion plays an important role in the treatment of patients with SCD, but it also causes iron overload on the other. It must be clarified whether the organ damage occurs as a result of the complications where treatment is attempted by exchange transfusion, or as a result of the iron overload caused by the exchange transfusion. The pain was reported as the most frequently observed complication in all SCD patients in a multicenter cohort study, in which it was also reported that patients who received iron chelator were less likely to experience pain and other complications (23, 24). In addition, the use of sufficient iron chelation treatment in SCD patients may prevent complications and also reduce morbidity and mortality (25). Notwithstanding the fact that iron chelation treatment has been widely recommended for use in SCD patients to date, a study conducted on 502 patients with SCD revealed that the use of iron chelation treatment in patients with SCD resulted in less efficacy, and thus more evidence is needed with regard to its safe use in patients with SCD (26). In our study, the use of iron chelators in SCD patients was not found to yield significant results in terms of the average life span (Tables 3, 4).

The limitations of our study include the fact that our study was a single–centered study that a sufficient number of patients could not be reached within the scope of our study and that the Hgb electrophoreses of the patients could not be checked. On the other hand, our study had superiority over other studies in the sense that we have divided the patients with SCD into two groups of SCD patients – those that experienced premature death and SCD patients that experienced late death – and that we have researched the efficacies of the methods to treat patients with SCD, those being hydroxyurea, an iron chelator, exchange transfusion, and surgery, based on the data obtained from these two groups.

CONCLUSION

Based on our findings, acute chest syndrome was the primary cause of death in SCD patients we have studied. Autosplenectomy was the most common complication observed in the SCD patients included in our study. In our study, the mean age of death was found to be lower compared to the mean age of death data reported in the literature. Use of hydroxyurea, use of iron chelator, exchange transfusion history, and surgical operation history due to SCD were not found to be significantly effective when the mean age of death reported in the literature was taken as the base value. There are different analyses in this sense provided in the literature, and we can have more insight only through further studies that will be carried out on this subject.

Ethics Committee Approval: The Mustafa Kemal University Clinical Research Ethics Committee granted approval for this study (date: 04.06.2020, number: 20).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MNK; Design – MNK; Supervision – MNK; Resource – MNK; Materials – MNK; Data Collection and/or Processing – MNK; Analysis and/or Interpretation – Gİ; Literature Search – Gİ; Writing – Gİ; Critical Reviews – Gİ.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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