Evaluation of the Most Common Complications of Sickle Cell Anemia and Management in Children: Simple Literature Review

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ABSTRACT

Background: Sickle cell anemia is an autosomal structural defect that affect the hemoglobin. It is associated with reduction in the RBC life span especially under stress. As a result of this structural defect the RBCs takes a sickle shape which is associated with a lot of complications that significantly have an effect on the patient's life.

Objective: In this study, we aim at evaluating the most common complication of sickle cell anemia. Also, the assessment of the various management plans to prevent it if occurred. **Methods:** PubMed database were used for articles selection as well as all relevant articles to our research interest with the following topics: Sickle cell anemia, Complications, Mortality, Prevention and Management. We excluded other articles, which are not related to this field. The data were extracted according to specific form in which it is going to be reviewed by the group members. **Conclusion:** Sickle cell anemia have various complications that have impact on quality of life and arise from effect of three main pathophysiological mechanisms i.e. Vasooclussive, hyper-haemolytic and infective complications. Hydroxyurea, chronic blood transfusion, and routine Transcranial Doppler Ultrasound are still the most useful preventive measures of SCA complications.

Keywords: Sickle cell anemia, complications, quality of life, children.

INTRODUCTION

Sickle cell anemia (SCA) is considered as one of the commonest gene disorder of human beings. In Africa, more than 200000 infants are born yearly with SCA [(1)]. In United States, mortality in SCA patients dramatically decreased with newborn screening and better comprehensive care. ***Powars et al.*** [(2)] found that the median age of sickle cell anemia patients is 53 years for men and 58 years for women[2]. Despite all of the progress that has been achieved in the medical management and care, still SCA patients are hospitalized frequently and by the fifth decade of life, 48% of surviving patients have documented irreversible organ damage [(2)]. SCA in Saudi Arabia was first reported in the Eastern province in the 1960s [(3)]. Since that time, a lot of studies have been done as for screening of SCA in Saudi Arabia regions. The Saudi Premarital Screening Program estimated the prevalence of the sickle cell gene in the adult population at 4.2% for sickle-cell trait and 0.26% for SCA, with the highest prevalence noted in the Eastern province (approximately 17% for sickle-cell trait and 1.2% for SCA [(4)].

Sickle cell anemia (SCA) is genetically inherited disease, in which there is a structural defect in the hemoglobin, associated with an amino acid substitution of valine for glutamic acid. As a result of this genetic defect the RBC life span will be shorter under stress and become sickle shape cells. The sickle shape RBC is the responsible for most of SCA complication. This happen because sickle shape RBCs are less deformable, therefore, they obstruct the microcirculation.

Complications of sickle cell anemia is a growing research area. As a result, we will revise the commonest complications of sickle cell anemia and evaluate the best measures to reduce it is occurrence.

MATERIALS AND METHODS

Sample

PubMed was chosen as the search database for the articles selection, because it is one of the major research databases within the suite of resources that have been developed by the National Center for Biotechnology Information (NCBI). The following topics were used: Sickle cell anemia, management, complications. The chosen articles were screened by titles, and reviewing the abstracts yielded 4 articles which were enrolled. **Inclusion criteria:** The articles were selected based on the relevance to the research project which should include one of the following topics {Sickle cell anemia, complications, mortality, prevention and control}. **Exclusion criteria:** all other articles which did not suit with these topics as their primary end, or repeated studies, and reviews studies.

Analysis

No software was used to analyze the data. The data extracted was based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes), these data were reviewed by the group. Double revision of each

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member's outcomes was applied to ensure the validity and minimize the mistakes.

RESULTS

We enrolled 10 studies according to our inclusion and exclusion criteria mentioned early. 5 of these studies were cohort studies, 3 randomize controlled trial, and 3 cross sectional study. All of these studies aimed at evaluating the various complications and management in sickle cell patients. The studies characteristics are shown in **Table 1.**

Study (year)	Study design	Objectives	Outcomes	Ref.
Matthew m. Heeney et al. (2015)	RCT	To assess the efficacy of prasugrel in reducing the rate of vaso-occlusive crisis, a composite end point of painful crisis or acute chest syndrome, in children and adolescents with sickle cell anemia.	The rate of vaso-occlusive crisis was not significantly lower among those who received prasugrel than among those who received placebo	(5)
Hamza Saidi et al.(2016)	Cross-sectional study	To evaluate the lifetime prevalence of SCA-related complications in children attending a tertiary care centre in Tanzania as well as the interventions used to treat children with SCA.	Children in Tanzania with SCD complication are diagnosed late, frequently hospitalized and have severe complications. Preventive therapies such as prophylactic penicillin, pneumococcal vaccination, and hydroxyurea are provision of proven. The burden of stroke is high and could be decreased through transcranial Doppler screening and transfusion therapy.	(6)
Tiago de Oliveira Boechat et al. (2015)	Retrospective cohort	- To determine the prevalence of DVT in children with SCD who are under the age of 12 years - To assess individual patients who had DVT to detect other risk factors that may have influenced the occurrence of thrombosis, such as the placement of a CVC.	Cvcs in children with SCD poses a high risk for DVT. The internal jugular vein should be utilized instead of the subclavian and femoral veins. The identification of associated risk factors may justify antithrombotic prophylaxis.	(7)
Azza Abdel Gawad Tantawy et al. (2014)	Cross sectional case-control study	To predict the severity of vascular complication in SCD patients by enos intron 4 gene polymorphism.	eNOS intron 4 gene polymorphism is related to endothelial dysfunction and vasculopathy in SCD and could provide utility for prediction of increased susceptibility to vascular complications.	(8)
Ikeoluwa Lagunju et al. (2015)	Cohort retrospective	To evaluate the effectiveness of hydroxyurea (HU) in reducing flow velocities in a cohort of Nigerian children with SCA and elevated velocities treated with HU.	HU appears to significantly reduce TCD velocities in Nigerian children with SCA and elevated velocities _170 cm/sec with beneficial effect on the haematological profile.HU may provide an effective approach to primary stroke prevention, particularly in Africa.	(9)
Leah D Vance et al. (2015)	Mixed retrospective-prospective observational cohort	To determine the interval after an initial ACS episode during which the majority of children <4 years old are re-hospitalized for ACS or severe pain.	The majority of children with ACS <4 years of age will be re-hospitalized for severe vaso-occlusive episodes within a year of an initial ACS episode.	(10)
Maria I. Cancio et al. (2015)	Retrospective cohort study	To assess the incidence rate of silent cerebral stroke in patients with SCA in early childhood.	Ischaemic cerebrovascular changes in very young children with SCA indicate greater risk of future overt and silent stroke. Children younger than 5 years may benefit from MRI/ MRA testing and should be considered for aggressive intervention when SCI are detected.	(11)

Study (year)	Study design	Objectives	Outcomes	Ref.
Russell E Ware et al. (2015)	RCT	To compare hydroxyurea with standard transfusions.	For high-risk children with sickle cell anaemia and abnormal TCD velocities who have received at least 1 year of transfusions, and have no MRA-defi ned severe vasculopathy, hydroxycarbamide treatment can substitute for chronic transfusions to maintain TCD velocities and help to prevent primary stroke.	(12)
Margaret T Lee et al. (2015)	Cross-sectional study	To examine the relationship between vitamin D levels and two of the most common acute vasoocclusive complications, acute pain and ACS.	There is high prevalence of vitamin D deficiency and its potential association with acute pain in SCD. Correcting low vitamin D may offer a simple, low-cost intervention to help reduce acute vaso-occlusive complications.	(13)
Ines Vaz Silva et al. (2014)	Retrospective cohort study	To analyze the chronic complications of SCD and look for predictive risk factors for increased severity and number of complications.	Leucocytosis and dactylitis in the first year of life can be predictors of SCD severity, while the presence of a-thalassemia can be protective. The determination of early predictors of chronic complications of SCD may improve the comprehensive care of these patients.	(14)

Heeney *et al.* [5] evaluated the efficacy of prasugrel in reducing the rate of vaso-occlusive crisis in children and adolescents with sickle cell anemia. According to a specific inclusion and exclusion criteria, a total of 341 patients (170 patients Palcepo group, 171 patients Prasugrel group) were enrolled in the study. They found that the rate of vaso-occlusive crisis events per person-year was 2.30 in the prasugrel group and 2.77 in the placebo group (rate ratio, 0.83; 95% confidence interval, 0.66 to 1.05). None of these differences were statistically significant (P = 0.12). Also, they found that the frequency of bleeding events requiring medical intervention, of hemorrhagic and non hemorrhagic adverse events that occurred while patients were taking prasugrel or placebo, and of discontinuations due to prasugrel or placebo, no significant difference happen between the two groups.

Saidi *et al.* [6] evaluated the lifetime prevalence of SCA-related complications in children attending a tertiary care center in Tanzania as well as the interventions used to treat them. According to a specific inclusion and exclusion criteria, a total of 124 participates included in the study. The period of study was between August 1, 2012 and September 30, 2012. Results showed that almost all participants (97.6%) had a prior history of a vaso-occlusive episode, 83 (66.9%) had prior acute chest syndrome, and 21 (16.9%) had prior stroke. In the preceding 12 months, 120 (96.8%) had been hospitalized, with a predominant vaso-occlusive episode as the main reason for hospitalization (35.5%). All of the included patients didn't receive hydroxyurea or penicillin. Preventive therapies should be considered , such as prophylactic penicillin, pneumococcal vaccination, and hydroxyurea. The risk of stroke is high and this could be decreased through the transcranial Doppler screening (TCD) and transfusion therapy.

Boechat *et al.* [7] evaluated the prevalence of deep venous thrombosis (DVT) in children with sickle cell disease who are under the age of 12 years and the risk factors that may influenced the risk of DVT. It is done over two years, a total 1063 were enrolled in the study according to specific inclusion and exclusion criteria. The result reported that 2 (0.2%) developed DVT with statistic significant of both cases being related to central venous catheters (CVCs) (P-value <0.001). The prevalence of DVT was 10% in patients who required CVCs. There was positive high correlation between CVC and increase risk of DVT. So, as preventive measurements internal jugular vein should be chosen instead of subclavian and femoral vein. Also, the identification of associated risk factors may justify antithrombotic prophylaxis.

Tantawy *et al.* [8] predicted the severity of vascular complication in SCD patients by eNOS intron 4 gene polymorphism. 51 patients with SCD recruited from the regular attendants of the Pediatric Hematology Unit with age ranged from 5 to 18 years were enrolled as a control group. They collected Peripheral blood samples on ethylene diamine tetra-acetic acid (EDTA) for complete blood count (CBC), hemoglobin analysis, and eNOS genotype. The distribution of eNOS alleles and genotypes was similar between patients with SCD and controls. Compared to bb genotype, the frequency of eNOS4a allele (aa and ab genotypes) was significantly higher in patients with elevated tricuspid regurgitant velocity (TRV) (P¼0.009), nephropathy (P¼0.006), or history of cerebral stroke (P¼0.029). Logistic regression analysis revealed that eNOS4a allele was an independent risk factor for elevated TRV (P<0.001). Patients with SCD and eNOS4a allele had higher level of lactate dehydrogenase, serum ferritin, D-Dimer, and von Willebrand factor antigen (P<0.05). eNOS intron 4 gene polymorphism is related to endothelial dysfunction and vasculopathy in SCD and could provide benefits for prediction of increased susceptibility to vascular complications in SCD patients.

Lagunju *et al.* [9] evaluated the effectiveness of hydroxyurea (HU) in reducing flow velocities in a cohort of Nigerian children with SCA. SCA patients, aged 2–16 years over a period of 4 years, were enrolled. All patients were offered routine transcranial Doppler (TCD) screening to determine stroke risk. The highest recorded mean velocity for each artery was assumed to be the most representative and this was recorded as the time-averaged mean of maximal flow velocities (TAMMV). Based on TAMMV reading, the results were classified into 3 groups: <170 cm/sec was regarded as normal, 170–199 cm/sec as conditional risk and _200 cm/sec, abnormal velocities. All children with abnormal TCD velocities _200 cm/sec were counseled for chronic blood transfusion (CBT) for primary stroke prevention. Those who declined CBT after repeated attempts at counseling and all those with CR velocities were placed on oral HU. Children on HU showed a statistically significant decline in mean velocities from 199.7 cm/sec to 165.8 cm/sec (P<0.001) with a significant increase in mean packed cell volume from 21.1 to 25.0 %. Children without treatment had a significant rise in mean velocities from 190.2 cm/sec to 199.7 cm/sec (P¼0.003). Children with conditional risk velocities on HU were less likely to convert to abnormal risk (P<0.001). The study showed the significant benefits of HU to reduce TCD velocities in Nigerian children with SCA with beneficial effect on the haematological profile. HU may provide an effective benefits to primary stroke prevention, particularly in Africa.

Vance *et al.* [10] determined the interval after an initial acute chest syndrome (ACS) episode during which the majority of children <4 years old were re-hospitalized for ACS. Children aged from 4 -18 were enrolled in the study. These children were followed for at least 3 years and cumulative prevalence of re-hospitalization for ACS or severe pain within 6 months, 1 years, and 2 years was calculated for children with an initial ACS episode <4 years old and compared to children with an initial ACS episode ≥4 years old. A total of 44.8% and 55.2% of participants had an initial ACS episode <4 years and ≥4 years old (Range: 4-17.7 years), respectively. At 1 year following the initial ACS episode, children <4 years old had a significantly higher cumulative prevalence of re-hospitalizations for ACS or pain as compared to children ≥4 years of age, 62.5% and 39.1%, respectively. The difference between the two groups was significant at P = 0.009. The most obvious finding to emerge from this study is that children with ACS <4 years of age re-hospitalized for severe vaso-occlusive episodes within a year of an initial ACS episode.

Cancio *et al.* [11] assessed the incidence rate of silent cerebral stroke in patients with SCA in early childhood. They reported clinical, neuroradiological, psychometric and academic follow-up over an average period of 14 years in 37 children with SCA who had magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain between ages 7 and 48 months. They found Ten patients (27%) younger than age 5 years (Group I) had SCI, as did 12 (32%) older than 5 years (Group II) and Fifteen (41%) had no lesions (Group III). Progressive MRI abnormalities, concurrent stenosis, decreased cognitive ability, attention/executive function deficits and hindered academic attainment were found commonly with group I. The proportions of subjects in Group I with subsequent neurological events (P ≤ 0_006), progressive ischemia (P ≤ 0_001) and vascular stenosis (P ≤ 0_006) were statistically significant and were greater than in Groups II and III. In general, therefore, it seems that ischaemic cerebrovascular changes in very young children with SCA indicate greater risk of future overt and silent stroke. When silent cerebral infracts are detected, this is indicate aggressive intervention to use MRI/ MRA testing in children younger than 5 years.

Ware *et al.* [12] done a randomized control trial to compare hydroxyurea with standard transfusions.

The study was conducted in the period between Sept 20, 2011, and April 17 Russell E Ware et al., 2013 with 159 patients enrolled in the study. These patients were screened and then randomly assigned to treatment, 61 patients received transfusion and 60 receive hydroycarbamide.

Final results of TCD velocities were: 143 cm/s (95% CI 140–146) in children who received standard transfusions and 138 cm/s (135–142) in those who received hydroxycarbamide, with a difference of 4 · 54 (0 · 10–8 · 98). For screening of new cerebral infracts at exit, Magnetic resonance brain imaging and angiography (MRI and MRA) were used with no new cerebral infracts in either treatment groups except in one case who received standards transfusion had worsened vasculopathy. Interestingly, the most common and serious adverse event in both group was vaso-occlusive pain (11 events in five [8%] patients with hydroxycarbamide and three events in one [2%] patient for transfusion). These results showed that high-risk children with sickle cell anaemia and abnormal TCD velocities who have received at least 1 year of transfusions, and have no MRA-defined severe vasculopathy, hydroxycarbamide treatment can substitute for chronic transfusions to maintain TCD velocities and help to prevent primary stroke.

Lee *et al.* [13] examined the relationship between vitamin D levels and two of the most common acute vasoocclusive complications, acute pain and ACS. Serum 25-hydroxyvitamin D (25-OHD) measured during comprehensive care examinations for 95 children with SCD along with history of acute pain and ACS within two years of obtaining 25-OHD was collected.

The results reported that Subjects were 3–20 years old (median 10.6); 48 males, 47 females; 46 African, 49 Hispanic; 72 SS, 20 SC, 1 S/b0Thalassemia, and 2 S/b Thalassemia. Median 25- OHD was 16 ng/ml. Fifty-six (59%) were vitamin D-deficient. Thirty one (33%) and 29 (31%) had at least one episode of pain and ACS, respectively. Serum 25-OHD was significantly associated with pain (P¼0.0121) but not with ACS (P¼0.628). Of those with pain, 73% (23/31) were vitamin D-deficient while 26% (8/31) had 25-OHD _20 ng/ml (P¼0.04, OR¼2.7, 95%CI¼1.05–6.94). There was strong relationship between vit.D deficiency and its potential association with acute pain in SCD. Elevation of the vitamin D level give a simple, low-cost intervention to reduce acute vaso-occlusive complications.

Silva *et al.* [14] analyzed the chronic complications of SCD and look for predictive risk factors for increased severity and number of complications. 80% of cases had chronic complication. They found that dilatation of the left ventricle was the most frequent complication (47.7%), followed by respiratory function disturbs (43.2%), microlithiasis or cholelithiasis (40.9%), increased flow velocity of cerebral arteries (31.8%), enuresis, delayed puberty and bone abnormalities (6.8% each), sickle cell retinopathy and leg ulcer (4.6% each) and recurrent priapism (2.3%). There was a significant positive correlation between leukocytes >15 000/lL and a higher number of hospitalizations ($P < 0.001$) and chronic complications of the disease ($P = 0.035$). Furthermore, A positive correlation was found between dactylitis in first year of life and higher number of hospitalizations ($P = 0.004$) and chronic complications ($P = 0.018$). Interestingly, the a-thalassemia was observed to have lower number of chronic complication ($P = 0.036$). One of the more significant findings to emerge from this study is that dactylitis and leukocytosis in the first year of life can predictor of SCD severity, while the presence of a-thalassemia can be protective. The determination of early predictors of chronic complications of SCD may improve the comprehensive care of these patients.

Sickle Cell Anemia Management

Proper management of sickle cell anemia (SCA) starts with establishing the right diagnosis at early years of life. The identification of infants that have been affected by neonatal screening programs that permits early initiation of prophylactic pneumococcal and penicillin immunizations, these vaccinations help to prevent overwhelming sepsis. Annual screening with transcranial Doppler ultrasonography is recommended for all children with sickle cell disease beginning at two years of age and continuing through adolescence to evaluate the risk of stroke and to initiate acute transfusion therapy in patients who are at high risk. Liberalized use of blood transfusions and early consideration of hydroxyurea treatment represent a new treatment essential for SCA management.

There is strong evidence to support the promotion and use of hydroxyurea therapy in patients nine months and older who have sickle cell anemia because its can decrease the frequency of vasoocclusive crises and acute chest syndrome with limited adverse effects.[22] Recently published guidelines provided important recommendations for health maintenance, acute care, and monitoring of disease-modifying therapy in persons with this condition.

Many patients with SCD do not receive routine preventive care recommended by the U.S. Preventive Services Task Force and immunizations recommended by the Advisory Committee on Immunization Practices. Persons with SCD also benefit from specialized condition-specific preventive strategies. Children with SCA are at increased risk of invasive pneumococcal disease due to ineffective spleen. In addition to the recommended pneumococcal vaccinations for all infants and children, those with SCA should receive prophylactic oral penicillin (125 mg twice daily for children younger than three years; 250 mg twice daily for those three years and older) once the diagnosis is established; this regimen should be continued until at least five years of age.[23] [24] Recommendations for prevention of SCA complication are summarized in Table 1.[24]

Common Acute and Chronic Complications

Concerns about drug-seeking behavior are widespread and often triggered by patients with SCD who have frequent VOCs that require potent opioid analgesics. These concerns should be addressed after adequately treating the acute pain. The use of an individualized VOC therapy plan that is carried with the patient and presented at urgent, emergency, or other care sites may lessen these concerns and facilitate rapid VOC management (Figure 1)[25]. Acute chest syndrome (ACS), defined as the presence of a new lung infiltrate in a patient with acute onset of lower respiratory symptoms such as cough and shortness of breath, is less common than VOC but potentially life threatening. In children, it often presents with fever and signs of middle lobe lung involvement, whereas adults are often afebrile and have multi lobe infiltrates. ACS can present on its own or as a complication of a VOC; it requires prompt evaluation and, once diagnosed, early intervention with antibiotic therapy and hospitalization[19].

Fever greater than 101°F (38.3°C), even in the absence of other signs of infection, needs to be assessed deliberately, because of absence or diminished splenic function, persons with SCD have a high risk of overwhelming bacterial infections or sepsis.[20] Fevers with conceivable infections should be treated empirically until culture results are available (Table 2).[18]

Disease-Modifying Therapies

Hydroxyurea works principally by increasing the level of fetal hemoglobin (HbF), which does not sickle. This enhances several clinical outcomes, for example diminishing the frequency of VOCs and ACS, reducing mortality, and decreasing the requirement for RBC transfusions and hospitalizations[21]. Table 3 and 4 summarize the recommendation of HU and acute transfusion in sickle cell disease patients[18].

Table 1. Preventive Strategies in Patients with SCD

Prevention of invasive pneumococcal disease
Administer prophylactic oral penicillin (125 mg for children younger than 3 years; 250 mg for children 3 years and older) twice daily until 5 years of age in all children with SCA. (SOR: strong, based on moderate-quality evidence)
Ensure that all persons with SCD have been vaccinated against *Streptococcus pneumoniae*. (SOR: strong, based on moderate-quality evidence)
Discontinue prophylactic penicillin in children with SCA at 5 years of age unless they have had a splenectomy or invasive pneumococcal disease. Ensure completion of pneumococcal vaccination series before discontinuation. (SOR: weak, based on moderate-quality evidence)
Ensure that children 6 to 18 years of age who have functional or anatomic asplenia have received at least 1 dose of 13-valent pneumococcal conjugate vaccine. (SOR: adapted from the Advisory Committee on Immunization Practices)
Screening for ischemic retinopathy
Refer patients with SCD to an ophthalmologist for an annual dilated retinal examination beginning at 10 years of age. (SOR: strong, based on low-quality evidence)
Rescreen persons with normal dilated retinal examination findings at 1- to 2-year intervals. (SOR: consensus)
Screening for renal disease
Begin annual screening of persons with SCD for microalbuminuria and proteinuria with spot urine testing by 10 years of age. (SOR: consensus)
Refer persons with proteinuria (> 300 mg per 24 hours) to a nephrologist for further evaluation. (SOR: strong, based on low-quality evidence)
Screening for vascular disease and stroke risk
Screen annually with TCD according to methods used in the STOP studies,* beginning at 2 years of age and continuing until at least 16 years of age. (SOR: strong, based on moderate-quality evidence)
Refer children with conditional (170 to 199 cm per second) or elevated (≥ 200 cm per second)

Table 1. Preventive Strategies in Patients with SCD

TCD findings to a subspecialist with expertise in long-term transfusion therapy aimed at preventing stroke. (SOR: strong, based on high-quality evidence)
Do not perform screening with CT or MRI in asymptomatic children with SCD. (SOR: moderate, based on low-quality evidence)
Do not perform screening with neuroimaging (TCD, CT, or MRI) in asymptomatic adults with SCD. (SOR: moderate, based on very low-quality evidence)
Do not perform screening with TCD in children with SCD but not SCA (e.g., HbSβ+-thalassemia, HbSC). (SOR: strong, based on low-quality evidence)

CT = computed tomography; Hb = hemoglobin; MRI = magnetic resonance imaging; SCA = sickle cell anemia; SCD = sickle cell disease; SOR = strength of recommendation; TCD = transcranial Doppler ultrasonography.

Table 2. Management of Acute Complications of SCD

ACS
Treat persons with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, and supplemental oxygen (to maintain oxygen saturation > 95%), and monitor for bronchospasm, acute anemia, and hypoxemia. (SOR: strong, based on low-quality evidence)
Encourage use of incentive spirometry while awake. (SOR: strong, based on moderate-quality evidence)
Consult an SCD expert regarding transfusion in persons with HbSC or HbSβ+-thalassemia who have ACS. (SOR: strong, based on low-quality evidence)
Perform urgent exchange transfusion in consultation with hematology, critical care, and/or apheresis subspecialists when there is rapid progression of ACS as manifested by oxygen saturation below 90% despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion. (SOR: strong, based on low-quality evidence)
Give simple blood transfusion (10 mL of red blood cells per kg) to improve oxygen-carrying capacity in persons with sickle cell anemia who have symptomatic ACS and whose hemoglobin concentration is > 1.0 g per dL (10 g per L) below baseline. If baseline hemoglobin is ≥ 9.0 g per dL (90 g per L), simple blood transfusion may not be required. (SOR: weak, based on low-quality evidence)
Priapism
Administer aggressive oral or intravenous hydration and oral or intravenous analgesia for episodes of priapism lasting 4 hours or longer. (SOR: strong, based on low-quality evidence)
Consult with a urologist for an episode of priapism lasting 4 hours or longer. (SOR: consensus)
Consult with a hematologist for possible preoperative transfusion if surgical intervention is required. (SOR: consensus)
Do not use transfusion therapy for immediate treatment of priapism associated with SCD. (SOR: moderate, based on low-quality evidence)
VOC
Initiate rapid treatment with parenteral opioids in adults and children with a VOC associated with severe pain. (SOR: strong, based on high-quality evidence)
Continue treatment with NSAIDs for adults and children with SCD who have a VOC associated with mild to moderate pain and who report relief with NSAIDs and do not have contraindications. (SOR: moderate, based on low-quality evidence)
Initiate around-the-clock opioid administration via patient-controlled analgesia or frequently scheduled doses vs. as-needed administration in adults and children with a VOC associated with severe pain. (SOR: moderate, based on low-quality evidence)
Use an individualized prescribing and monitoring protocol (written by the patient's primary physician for SCD care) or an SCD-specific protocol whenever possible to promote rapid, effective, and safe analgesic management and resolution of the VOC in children and adults with SCD (Figure 1). (SOR: consensus)
To reduce the risk of ACS, encourage the use of incentive spirometry while awake in adults and children who are hospitalized for a VOC. (SOR: strong, based on moderate-quality evidence)
Do not give blood transfusions to children and adults with a VOC unless there are other indications. (SOR: moderate, based on low-quality evidence)

ACS = acute chest syndrome; Hb = hemoglobin; NSAID = nonsteroidal anti-inflammatory drug; SCD = sickle cell disease; SOR = strength of recommendation; VOC = vasoocclusive crisis.

Table 3. Recommendations for Hydroxyurea Therapy in Patients with SCD

Beginning at 9 months of age, counsel all patients with SCA and their families about hydroxyurea therapy. (SOR: consensus)
Initiate hydroxyurea therapy in adults with SCA who have 3 or more sickle cell–associated moderate to severe pain crises in 12 months. (SOR: strong, based on high-quality evidence)
Initiate hydroxyurea therapy in adults with SCA who have a history of severe or recurrent acute chest syndrome. (SOR: strong, based on moderate-quality evidence)
Initiate hydroxyurea therapy in adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life. (SOR: strong, based on moderate-quality evidence)
Initiate hydroxyurea therapy in adults with SCA who have sickle cell– associated pain that interferes with daily activities and quality of life. (SOR: strong, based on moderate-quality evidence)
Offer hydroxyurea therapy for children 9 months and older who have SCA, regardless of clinical severity, to reduce SCD-related complications (e.g., pain, dactylitis, acute chest syndrome, anemia). (SOR for children 9 to 42 months of age: strong, based on high-quality evidence; SOR for children older than 42 months: moderate, based on moderate-quality evidence)
Use an established prescribing and monitoring protocol to ensure proper use of hydroxyurea therapy and to maximize its benefits. (SOR: strong, based on high-quality evidence)
Consider adding hydroxyurea therapy to improve anemia in adults and children with SCD and chronic kidney disease who are receiving erythropoietin. (SOR: weak, based on low-quality evidence)
Consult a sickle cell expert for consideration of hydroxyurea therapy in patients with HbSβ+-thalassemia or HbSC who have recurrent sickle cell– associated pain that interferes with daily activities or quality of life. (SOR: moderate, based on low-quality evidence)
Consult a sickle cell expert if a patient does not have a clinical response to appropriate doses and duration of hydroxyurea therapy. (SOR: moderate, based on very low-quality evidence)
Discontinue hydroxyurea therapy in pregnant or breastfeeding women. (SOR: moderate, based on very low-quality evidence)

Hb = hemoglobin; SCA = sickle cell anemia; SCD = sickle cell disease; SOR = strength of recommendation.

Table (4). Recommendation for Blood Transfusion in Patients with SCD

Type of transfusion	**indication of acute transfusion**
• Simple	Symptomatic ACS and decreased hemoglobin of 1.0 g per dL (10 g per L) below baseline (SOR: weak, based on low-quality evidence)
• Exchange	Symptomatic severe ACS (oxygen saturation < 90% despite supplemental oxygen; SOR: strong, based on low-quality evidence)
• Simple	Acute splenic sequestration and severe anemia (SOR: strong, based on low-quality evidence)
• Simple or exchange	Stroke (SOR: moderate, based on low-quality evidence)
• Simple	Aplastic crisis (SOR: consensus)
• Simple or exchange	Hepatic sequestration (SOR: consensus)
• Simple or exchange	Intrahepatic cholestasis (SOR: consensus)
• Simple or exchange	Multisystem organ failure (SOR: consensus)
• Simple	Symptomatic anemia (SOR: consensus)
• **Contraindications**	
• Asymptomatic anemia (SOR: consensus)	
• Priapism (SOR: moderate, based on low-quality evidence)	
• Uncomplicated painful crisis (SOR: moderate, based on low-quality evidence)	

ACS = acute chest syndrome; SOR = strength of recommendation.

DISCUSSION

Sickle cell disease is a genetic disorder that cause a structural defect in the hemoglobin. As a result of this structural defect the patients RBC takes sickle shape which can block the microcirculations and cause various complications. As a result of this we intended to evaluate these complications and the various measures that can be done to manage it.

By looking at the included studies we found that Sickle cell anemia have various complications that have impact on the quality of life and arise from

effect of three main pathophysiological mechanisms i.e. vaso-occlusive, hyper-haemolytic and infective complications. The vaso-occlusive complications include silent cerebral stroke, acute chest syndrome, priapism, splenic sequestration, liver diseases, leg ulcers, osteomyelitis, retinopathy, renal insufficiency. Hemolytic complications include anemia, cholelithiasis and aplastic and megaloblastic crises. Infective complications could result from viral, bacteria, fungal and atypical microorganisms but common ones include encapsulated organisms like Streptococcus pneumonia infections, bacteria causing chronic osteomyelitis and E. coli sepsis especially in children.

Saidi *et al.* [6] found that the majority of SCA patient's complications are vaso-occlusive episode, acute chest syndrome, and a few number of patients developed strokes respectively. Also, they found that the most significant cause of re-hospitalization is vaso-occlusive crisis. **Cancio *et al.*** [11] evaluated the effect of silent strokes in SCA patients. They found that patients who developed stroke at age below 5 years had significant reduction in their mental function and brain capabilities, also they advised that when silent cerebral infracts are detected, this indicates aggressive intervention to use MRI/ MRA testing in children younger than 5 years. In children with SCD, the routine use of transcranial Doppler (TCD) screening along with chronic transfusion therapy has decreased the prevalence of overt stroke from 11% to 1% [16]. **Saidi *et al.*** [6] mentioned that stroke risk could be decreased through the transcranial Doppler screening (TCD) and transfusion therapy. **Lagunju *et al.*** [9] mentioned that the increase in the blood flow velocity increases the risk of silent strokes in SCA patients. They advised for the use of hydroxyurea in SCA patients which could provide an effective benefits to primary stroke prevention. **Ware *et al.*** [12] advised that patients with high risk of getting strokes may benefit better form the standard blood transfusion. **Vance *et al.*** [10] explained that most of SCA patients developed their first acute chest syndrome (ACS) attacks after the age of 4 years, but they also, found that patients who get their first attack of acute chest syndrome younger than 4 years are at more risk for re-hospitalization in the future for the same symptoms. So, patients' with history of development of ACS under 4 years needs further evaluations and more follow up visits with their pediatricians to avoid undesirable complications. **Silva *et al.*** found that dactylitis and leukocytosis (>15 000/lL) in the first year of life can be apredictor of SCA severity, while the presence of alpha thalassemia can be protective. The determination of early predictors of chronic complications of SCD may improve the comprehensive care of these patients. **Oliveira *et al.*** [7] discussed the risk of development of deep venous thrombosis (DVT) in SCA patients and the factors that may have an influence in escalating it is incidence. They found that SCA per se does not induce an influence in development of DVT, but having a Central venous catheter insertion in SCA patients significantly increase the risk. So, as preventive measurement internal jugular vein should be chosen instead of subclavian and femoral vein. Also, the identification of associated risk factors may justify antithrombotic prophylaxis. **Tantawy *et al.*** [8] tried to assess the relation between the genetic mutations in SCA patients and the rate of development of vascular complications. Interestingly, they found that eNOS intron 4 gene polymorphism was related to endothelial dysfunction and vasculopathy in SCD. This can help in prediction of patients with increased susceptibility to vascular complications. Further literatures surveys have to be intensified in this area which could help in reduction in one of the most important SCA complications. One of the most common causes of SCA patient's visits for emergency department is acute pain. **Lee *et al.*** [13] found that acute pain is strongly related to the level of vitamin D. As a result, they advised doing measurement of vitamin D in every SCA patients that usually visit ER for acute pain symptoms.

The main treatments for SCA patients are HU and chronic blood transfusion. Red blood cell transfusions can be administered by simple or exchange transfusion. There is many indications for transfusion therapy: Acute ischemic stroke, Primary stroke prevention, Secondary stroke prevention, Acute chest syndrome (acute), Acute splenic sequestration, Preoperative and other [24]. **Ribeil *et al.*** [25] published a case report in 2017, about a sickler patient who was treated with antisickling β-globin gene into autologous hematopoietic stem cells [25]. The most interesting finding was that antisickling β-globin remained high (approximately 50% of β-like–globin chains) without recurrence of sickle crises and with correction of the biologic hallmarks of the disease after fifteen months of treatment.

Strengths and Limitations

During articles selection, we doubled-reviewing the studies, and their results to assure that we enrolled the studies related to our aim, and to avoid any errors in the results. We acknowledge the limitations we had done in this study. We tried to

include articles that fit with our outcome criteria for inclusion into our review. Certainly, a bigger sample size would provide more significant results.

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