Vol 6|Issue 2| 2016|99-105.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

A CASE STUDY ON SICKLE CELL ANAEMIA WITH DACTYLITIS PHARMACIST INTERVENTION AND PATIENT COUNSELLING

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ABSTRACT

Sickle cell anemia (sickle cell disease) is a disorder of the blood caused by an inherited abnormal hemoglobin. The abnormal hemoglobin causes distorted (sickled) red blood cells. The sickled red blood cells are fragile and prone to rupture. vaso-occlusive crisis in sickle cell anemia include dactylitis, priapism, abdominal pain, and jaundice. Dactylitis or sausage digit is inflammation of an entire digit (a finger or toe), and can be painful. Present case was admitted with the chief complaint of Sickle cell anaemia with Dactylitis. On treatment patient was presented with a side effect of cloudy urine which is the common side effect due intake of paracetamol or amikacin for long period but here the patient was given with both drugs at same time so the patient exhibited cloudy urine. Therefore the frequency of paracetamol of decreased and counselling was given to the patients representative that it is only due to use of drugs and will not be seen on discontinuation of drugs. Later, on treatment the patient was found to be coherent, decreased joint pains, swelling of toes, reduced pallor, responding to therapy and discharged by giving discharge medication. As the patient is pediatric, her mother was counselled about the disease state and importance of medication adherence.

Key words: Sickle cell anaemia, Dactylitis, Paracetamol, Amikacin.

INTRODUCTION

Sickle cell disease refers to the group of disorders that affects haemoglobin to form abnormal haemoglobin molecules (HbS). Sickle cell anaemia is the name of the specific form of sickle cell disease in which there is homozygosity for the mutation that causes HbS (ie HBSS).

Sickle cell haemoglobin (HbS) results from an autosomal recessively inherited mutation in which the 17th nucleotide of the beta globin gene is changed from thymine to adenine and the amino acid glutamic acid is replaced by valine at position 6 in the beta globin chain [1, 2]. Sickle cells have a reduced deformability and are easily destroyed, causing occlusion of the microcirculation and a chronic haemolytic anaemia with a median haemoglobin concentration level of about 9 g/dL. Sickling disorders include heterozygous (AS) sickle cell trait, homozygous (SS) sickle cell disease, compound heterozygous states for HbS with haemoglobins C, D, E, or other structural variants and the combination of the sickle cell gene with different forms of thalassaemia [3].

Dactylitis, or hand-foot syndrome, is commonly the first clinical manifestation of sickle cell disease. Typically the child cries with pain, refuses to bear weight and has puffy, tender and warm feet or hands or both [4-7].

Etiology and Epidemiology

Sickle cell disease (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited hemoglobinopathy, which results in the hallmark clinical sequelae of vasoocclusive phenomena and hemolysis. The genetic abnormality is due to a substitution of the amino acid valine for glutamic acid at the sixth position on the beta globin chain and was first described over one hundred years ago [8] Hemoglobin S (HbS), the hemoglobin that is produced as a result of this defect, is a hemoglobin tetramer (alpha2/beta S2) that is poorly soluble and polymerizes when deoxygenated [9]. Overall, the incidence of sickle cell disease exceeds that of most other serious genetic disorders, including cystic fibrosis and haemophilia [10]. It is seen worldwide but occurs most frequently in Africans and less

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commonly in those of Mediterranean, Latino, East Indian, and Arab descent [11]. It is estimated that 16% of the population in Africa has a sickle hemoglobinopathy which is the highest proportion worldwide. The Americas and the East Mediterranean region represent the next highest proportion of sickle cell hemoglobinopathy as delineated by the World Health Organization [11].

Pathophysiology

There is a large amount of heterogeneity in the expression of sickle cell disease which is not fully explained by the single mutation or different variants of hemoglobin S. This variability is manifest by a wide spectrum in both frequency and intensity of painful vaso-occlusive crises as well as highly variable degrees of organ dysfunction. The pathophysiologic processes that lead to sickle cell disease related complications result from a combination of hemolysis and vaso-occlusion. Hemolysis occurs as a result of repeated episodes of hemoglobin polymerization/depolymerization as sickle red blood cells pick up and release oxygen in the circulation. Red blood cell membranes become abnormal from this process and red blood cells have a shortened lifespan. Hemolysis can occur both chronically and during acute painful vaso-occlusive crises and also results in the release of substantial quantities of free hemoglobin into the vasculature. This resultant free ferrous hemoglobin likely consumes significant quantities of nitric oxide (NO), which in turn, leads to abnormal regulation in vascular homeostasis [12-14]. In addition to hemolysis, intermittent episodes of vascular occlusion cause tissue ischemia, a major morbid component of the disorder which results in acute and chronic multi-organ dysfunction [15] and which is characterized by chronic inflammation and ischemia-reperfusion injury [16-18]. Data suggest that neutrophils play a key role in the tissue damage which occurs as both neutrophil numbers are increased and evidence suggests that they are abnormally activated and adherent [19]. Likewise, recent data suggest that sickle red cells induce adhesion of lymphocytes and monocytes to the endothelium such that these may contribute to the pathogenesis of vascular occlusion [20].

Signs and Symptoms

The symptoms of sickle cell disease can begin between 3 months and 6 months of age when HbF levels are falling.

- Anaemia, jaundice, pallor, lethargy, growth restriction and general weakness; the most common causes of anaemia are acute splenic sequestration, transient red cell aplasia, and hyperhaemolysis in patients with severe infection.
- Increased susceptibility to infections by encapsulated bacteria such as pneumococcus; the risk of overwhelming infection is highest before the age of 3 years.
- Splenomegaly may be present in infancy and childhood but recurrent splenic infarcts then cause autosplenectomy.
- Delayed puberty.

Complications

- Sickle cell disease is very variable in its manifestations. The pattern of organ involvement alters with age.
- Chronic pain.
- Nocturnal enuresis [4].

Infection

Patients are prone to infection, especially pneumococcus, typhoidosteomyelitis and haemophilus because of hyposplenism resulting from sickling and consequent autosplenectomy [4].

Stroke

Clinical evidence of stroke occurs by age 20 years in 11% of patients with sickle cell disease.

Priapism

Males with sickle cell disease may experience painful erections, which may be brief but recurrent or may last six hours or more and can lead to impotence.

Cardiac failure

Left-sided heart disease occurs in about 13% of adults with sickle cell disease and is mainly caused by diastolic dysfunction, which is an independent risk factor for mortality [4].

Chronic pulmonary disease usually develops in patients older than 30 years. Cor pulmonale may develop. Pulmonary hypertension occurs in about 30% of adults with sickle cell disease and is associated with high rates of leg ulcer, priapism, and renal dysfunction. Gallstones caused by chronic haemolytic anaemia.

- Eye: retinopathy, retinal infarcts, retinal haemorrhage and retinal detachment.
- Transfusion complications: alloimmunisation, exposure to possible infections, risk of iron overload and consequent organ damage [4].
- Chronic leg ulcers: may become infected.
- Avascular necrosis is a frequent and severe complication of sickle cell disease [21]. It often affects the femoral head and humeral head.
- Chronic organ damage: vaso-occlusion, hyperhaemolysis, and increased blood viscosity are major causes of chronic organ damage (osteonecrosis, liver failure, renal failure, leg ulcer, retinopathy), which is very variable in severity.
- Chronic kidney disease: causes a worsening anaemia and may require treatment with high doses of erythropoietin.
- Learning difficulties:
- Subtle, but important and widespread, neuropsychological defects result from sickle cell disease and may be present even in the absence of overt neurological complications.
- This damage is probably responsible for the decreased intellectual ability of about five points in IQ in patients with sickle cell disease compared with controls.

- This reduction indicates an increased risk for significant learning difficulties and the need for remedial education compared with their peers [22, 23].

Differential Diagnosis

- Other causes of haemolytic anaemia.
- Acute pain: assess all patients with sickle cell disease who present with acute pain to determine whether their pain is being caused by an acute painful sickle cell episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical [24].

Investigations

FBC and blood film: the haemoglobin level is in the range 6-8 g/dL with a high reticulocyte count of 10-20%; the blood films may show sickled erythrocytes and features of hyposplenism. Sickling of red cells on a blood film with 2% sodium metabisulphite.

Sickle solubility test: a mixture of HbS in a reducing solution such as sodium dithionite gives a turbid appearance because of precipitation of HbS, whereas normal haemoglobin gives a clear solution.

Haemoglobin analysis (eg, by electrophoresis) is always needed to confirm the diagnosis. There is no HbA, 80-95% HbSS, and 2-20% HbF.

Sickle cell trait is diagnosed by the finding of a positive sickling test together with haemoglobins A and S on electrophoresis [25]. Other investigations such as renal function tests, LFTs and lung function tests should also be performed at diagnosis (baseline) and routine monitoring. Other investigations will depend on any complications - eg, infection screen, abdominal ultrasound, CT scan of the head (eg, if a subarachnoid haemorrhage is suspected).

Screening

Neonatal screening programmes that can identify children with sickle cell disease before they present with potentially fatal sepsis. Heel prick blood spots are usually collected 3 to 10 days after birth and haemoglobin analysed. This reliably identifies affected babies and allows penicillin to be started by 3 months of age [25]. Preconceptual testing for haemoglobinopathies is recommended in at-risk groups [26].

- Policies for antenatal and neonatal screening vary throughout the UK [27].
- Pre-operative screening for sickle cell disease should be carried out in patients from ethnic groups in which there is a significant prevalence of the condition. Emergency screening with sickle solubility tests must always be followed by definitive analysis.
- Prenatal diagnosis: sickle cell disease can also be diagnosed in a fetus through prenatal diagnosis (following genetic counselling) from amniocentesis, chorionic villus sampling and fetal blood [27].

INDICATIONS FOR URGENT REFERRAL TO HOSPITAL IN SICKLE CELL DISEASE

- Severe pain not controlled by simple analgesia or low-dose opioids.
- Dehydration caused by severe vomiting or diarrhoea.
- Severe sepsis: temperature >38.5°C or >38°C if under 2 years old, temperature <36°C, or hypotension.
- Symptoms or signs of acute chest syndrome including tachypnoea, oxygen saturation more than 5% below steady state, signs of lung consolidation.
- New neurological symptoms or signs.
- Symptoms or signs of acute fall in haemoglobin.
- Acute enlargement of spleen or liver over 24 hours, particularly in young children.
- Marked increase in jaundice.
- Haematuria.
- Fulminant priapism lasting more than two hours or worsening of recurrent episodes

Prognosis

Clinical severity and prognosis are very variable, ranging from survival into the 60s and 70s to a severe disease with substantial organ damage and early death. Median life expectancy is currently 40-60 years in high-income countries but much less in low-income areas. The most common cause of death in the first two years of life is infection, with or without splenic sequestration. In adults, common causes of death are cerebrovascular accidents, sepsis, acute chest syndrome and pulmonary hypertension [28].

Treatment

Folic acid supplementation may be required. Zinc supplementation should also be considered if growth is restricted. Vitamin D deficiency is very prevalent in non-white children in the UK and may co-exist with sickle cell disease, so advice should be given regarding vitamin supplementation [29].

Psychological

Good support of patients, families and other carers is essential. Cognitive behavioural therapy may be indicated.

Infection

Oral penicillin prophylaxis is started at diagnosis. The risk of pneumoccocal infection remains high but decreases with age. There is a steady rise in prevalence of penicillin-resistant pneumococci. Penicillin prophylaxis is continued throughout life in some countries but is stopped at age 5 years in other countries. Routine childhood vaccinations include protection against *Haemophilus influenzae* type B and conjugated vaccines against *Streptococcus pneumoniae* in most high-income countries. Children should also receive unconjugated pneumococcal vaccine from 2 years of age, repeated every three to five years, and immunisation against meningococcus, influenza, and hepatitis B. Because malaria is a significant cause of morbidity and mortality in patients with sickle cell disease, malaria chemoprophylaxis is often recommended [30]

Blood transfusions

Transfusion therapy is a key intervention in decreasing morbidity and mortality in patients with sickle

cell disease [31]. Transfusion may be required for severe anaemia or to reduce the proportion of HbS if there are lung or central nervous system complications. Partial exchange transfusion (rather than top-up transfusion) is indicated when it is necessary to reduce the percentage of haemoglobin S quickly in acute life-threatening complications, such as severe acute chest syndrome, acute stroke, multi-organ failure or urgent preparation for major surgery. Iron overload is a possible complication of regular transfusions and iron chelation should be started in all children receiving regular blood transfusions [29].

Hydroxycarbamide (hydroxyurea)

Many cytotoxic drugs increase fetal haemoglobin concentrations, which is potentially beneficial for patients with sickle cell disease. Benefits include increasing haemoglobin concentrations, and decreasing platelet and white cell counts. Concerns remain about its myelosuppressive and teratogenic effects and its possible long-term toxicity. Hydroxycarbamide (hydroxyurea) should be stopped at least three months before conception [32].

- Hydroxyurea can reduce:
- The frequency of crises in sickle cell disease.
- The episodes of acute chest syndrome
- The need for blood transfusions. It is not yet licensed for use in sickle cell disease.

It should still be used only on a named patient basis with close haematological supervision.

Bone marrow transplantation

Haematopoietic stem cell transplantation is potentially curative but is currently used only in patients with a severe clinical course and a matched sibling donor. Its use is limited by the toxicity and the availability of suitable donors.

Stroke

Stroke prevention: it is recommended that transcranial Doppler ultrasonography be performed annually in children aged 2-16 years with sickle cell disease and that regular blood transfusions should be considered in those with abnormal findings on transcranial Doppler ultrasonography.

Assessment and prevention of nocturnal hypoxia (obstructive sleep apnoea) when relevant may be important in preventing strokes. Exchange transfusion should be performed when a stroke occurs. Stroke is considered an indication for bone marrow transplantation in children and adolescents who have siblings with identical HLA.

Treatment of acute chest syndrome

Treatment includes inspired oxygen, incentive spirometry (also used for pain crises with back or chest pain), continuous positive airways pressure and exchange transfusion. Occasionally ventilation may be necessary. Antibiotics are given using a combination of a macrolide with intravenous cephalosporin.

Transfusion or exchange transfusion produced improvements in several uncontrolled studies. Hydroxycarbamide decreased the episodes of acute chest syndrome in one multicentre study. Periodic transfusion is also effective in preventing recurrences.

Treatment of priapism

- Priapism is an emergency requiring hydration and analgesia.
- In minor episodes, bladder emptying, exercise such as jogging, warm baths and analgesia may help abort an attack.
- Oral etilefrine may reduce the frequency of stuttering priapism.
- In a prolonged episode, aspiration and irrigation of the corpora cavernosa with adrenaline (epinephrine) or etilefrine is now the treatment of choice.
- Children and their carers should be advised to seek treatment early and should attend hospital as an emergency if priapism persists for more than two hours.

Contraception

- Hormone and barrier methods are all acceptable choices but intrauterine devices are not recommended, as they may be associated with uterine bleeding and infection.
- Depot contraceptive (Depo-Provera®) is safe and has been found to improve the blood picture and reduce pain crises [33].

PAINFUL CRISES

Many episodes of uncomplicated acute pain can be managed at home with simple analgesia and community support [24]. Pain experienced in a vaso-occlusive crisis results from oxygen deprivation of tissues and avascular necrosis of the bone marrow. Dactylitis is a common early manifestation that may occur before the age of 6 months. It is uncommon after 2 years of age [24].

The risk of vaso occlusive episodes is increased by exposure to cold, fever, and dehydration. Over 90% of hospital admissions for patients with sickle cell disease are for painful crises, but nearly all sickle pain is coped with in the community. Pain has been reported to occur on up to 30% of days with a loss of 10% of schooldays in children. Hydroxycarbamide can reduce the frequency of painful crises in sickle cell disease (unlicensed indication in the UK) [30]

Management

Avoid exposure to cold, fever, dehydration and stress. Most episodes coped with at home respond to simple oral analgesia, increased fluid intake, warmth and rest. A simple analgesic ladder is appropriate, starting with paracetamol and/or ibuprofen [29]. If necessary, use weak opioids (eg, codeine or dextropropoxyphene) for patients with mild pain. Always look for a cause - eg, infection. Admit patients if pain does not subside promptly, if there is a need for strong opioid treatment, or if fever, pallor or signs of respiratory compromise are noted [3].

Parental and Patient Education

- Avoiding situations that can precipitate crises (eg, cold, dehydration, and exhaustion) and early recognition and treatment of infection.
- Palpation for splenic size to ensure early presentation of splenic sequestration can significantly reduce deaths.
- All patients should be advised to avoid alcohol because of its dehydrating effects and smoking because it may cause the acute sickle chest syndrome [29].

CASE STUDY

A patient of 3 years old female born out of non-consanguineous marriage with a weight of 10.5kg and height of 50cm was admitted in King George Hospital, Visakhapatnam, Andhra Pradesh, India by her mother with a complaint of severe joint pains since 2days.

History of present illness includes patient was apparently normal 2 days ago, complaint started as sudden onset of joint pains all over the body, predominantly over the interphalangeal joints of hands. There is a past medical history of known case of sickle cell anaemia advised for blood transfusions every month. There is a history of only one blood transfusion. Personal history of the patient includes mixed diet, normal appetite, normal bowel and bladder habits. Immunisation history includes immunised as per USP schedule. Developmental history includes achieved mile stones as per age. On admission his body temperature was normal, PR 105beats/min, RR 32beats/min, CRT 2seconds, pallor was seen. Laboratory investigations included as Hb 7.2gm%, total leucocyte count 9000cells, differential leukocyte count-polymorphs 63% lymphocytes 30% basophils 7%,ESR 35mm/1st hour, packed cell volume 25%, platelets count 1.2lakhsRandom blood sugar 96gm/dl, blood urea nitrogen 40mg%,Serum sodium 139 mmol/lit, Serum calcium 3.45 mmol/lit.

From the subjective findings of joint pains, known case of sickle cell anaemia and objective findings of abnormal Hb, PCV, ESR the present case was finally diagnosed as Sickle cell anaemia with dactylitis.

On 1st day PR was 105bpm,RR was 32bpm and CRT was 2 secs. So the treatment was given with IVF-500ml RL at 20µl/min over 2 hrs to compensate body fluid levels, Inj.Cefotaxime 500mg IV TID which is an antibiotic used to treat and prevent infections, Inj.Amikacin 70mg IV BD which is an antibiotic used to treat prevent infections and Syp.PCM-125(paracetamol) 6ml QID which is a non-steroidal anti inflammatory drug used to reduce pain and to maintain body temperature. Oral feeds were give with plenty of water.

On 2nd day PR was 110bpm, RR was 24bpm, CRT was 2 sec. So given with Inj. Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125(paracetamol) 6ml QID, Oral feeds were give with plenty of water. On 3rd day PR 110bpm, RR 24bpm, CRT 2sec and patient complained of cloudy urine. We the clinical pharmacist trainees suspected that cloudy urine may be due to concomitant use of Inj.Amikacin and Syp.PCM. So we discussed with the physicians asked to reduce the frequency of paracetamol from QID to TID which is enough for effective treatment of the patient. We also counselled the patient that the side effect is only due to intake of the drugs and will not be seen after discontinuation of the drugs. The treatment was given with Inj.Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125(paracetamol) 6ml TID, Oral feeds were give with plenty of water, B+ve blood transfusion was done.

On 4th day PR 100bpm,RR 22bpm,CRT less than 2secs, pallor was reduced. So the treatment was given with Inj.Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125(paracetamol) 6ml TID, Oral feeds were give with plenty of water. Tab.Deferasirox 125mg which is a chelating agent binds to iron and removes it from the blood stream.

On 5th day PR 95bpm,RR 22bpm,CRT less than 2secs, no pallor. So the treatment was given with Inj.Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125(paracetamol) 6ml TID, Tab.Deferasirox 125mg, Oral feeds were give with plenty of water.

On 6th day PR 95bpm,RR 20bpm,CRT less than 2secs, no pallor. So the treatment was given with Inj.Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125 (paracetamol) 6ml TID, Tab.Deferasirox 125mg, Oral feeds were give with plenty of water.

On 7th day PR 90bpm,RR 20bpm,CRT less than 2secs, no pallor. So the treatment was given with Inj.Cefotaxime 500mg IV TID, Inj.Amikacin 70mg IV BD, Syp.PCM-125(paracetamol) 6ml TID, Tab.Deferasirox 125mg, Oral feeds were give with plenty of water. The patient was stable with decreased swelling and pain in the foot, reduced joint pains, no pallor. So discharged by giving medication and counselling was done to the patient's representative about the disease and proper use of drugs and a patient information leaflet is given.

Discharge Medication

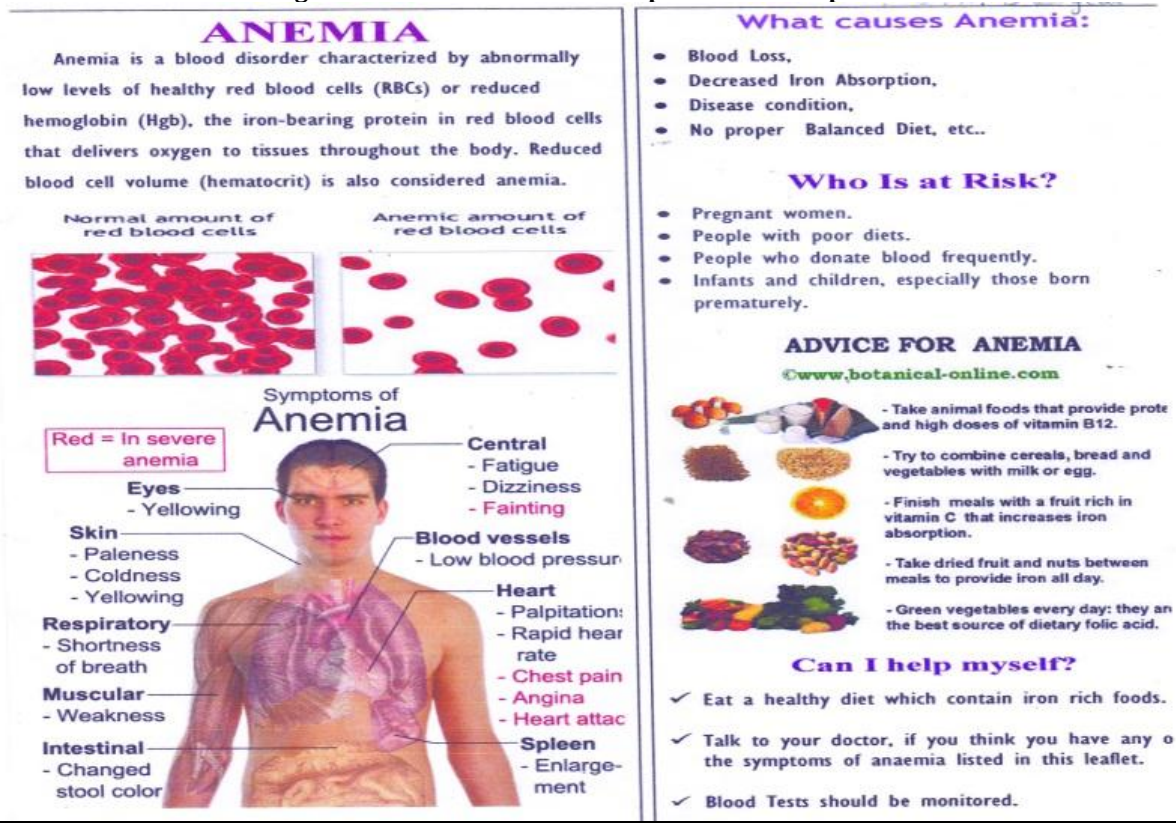
Tab.BC(vitamin b complex) OD
Tab. Folic acid OD
Tab. Deferasirox OD

Table 1. Therapy

DAY	TREATMENT
Day1	Intravenous fluids-ringer lactate 500ml at 20µl/min over 2 hrs Inj.Cefotaxime 500mg IV TID Inj.Amikacin 70mg IV BD Syp.PCM-125(paracetamol) 6ml QID Oral feeds were give with plenty of water
Day2	Inj.Cefotaxime 500mg IV TID Inj.Amikacin 70mg IV BD

	Syp.PCM-125(paracetamol) 6ml QID Oral feeds were give with plenty of water
Day3	Inj.Cefotaxime 500mg IV TID Inj.Amikacin 70mg IV BD Syp.PCM-125(paracetamol) 6ml TID Oral feeds were give with plenty of water B+ve Blood transfusion was done
Day4,5,6,7	Inj.Cefotaxime 500mg IV TID Inj.Amikacin 70mg IV BD Syp.PCM-125(paracetamol) 6ml TID Oral feeds were give with plenty of water

Fig 1. Patient information leaflet provided to the patient



CONCLUSION

Sickle cell anemia is an inherited form of anemia which is a condition in which there aren't enough healthy red blood cells to carry adequate oxygen throughout the body. In sickle cell anemia, the red blood cells become rigid and sticky and are shaped like sickles or crescent moons. These irregularly shaped cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to parts of the body. There's no cure for most people with sickle cell anemia. However, treatments can

relieve pain and help prevent further problems associated with sickle cell anemia like infections, pain, acute chest syndrome, stroke, dactylitis, priapism. In the present case, treatment with Intravenous fluids-ringer lactate 500ml, Inj.Cefotaxime 500mg, Inj.Amikacin 70mg, Syp.PCM-125, Blood transfusion, patient showed positive prognosis after a long duration of therapy for 7 days. As a clinical pharmacist we have done the TDM and drug utilisation review for the patient for the occurrence of any drug related side effects or drug interactions and for positive prognosis of the patient with the collaborative efforts of physician, clinical pharmacist and nursing staff. During treatment patient was presented with a side During the treatment, patient complained of cloudy urine which is a common side effect of paracetamol and amikacin when taken for longer period. Here, as the patient was given with both paracetmol and Amikacin at a time, cloudy urine was seen. So, the frequency of paracetamol was decreased and counselling was given to the patients representative that it is only due to use of drugs and will not be seen on discontinuation of drugs. Later, Patient exhibited positive prognosis and discharged with medication Tab.BC(vitamin b complex) OD, Tab. Folic acid OD, Tab. Deferasirox OD. Patient representative was counselled about the disease, proper use of medications, diet to be taken and life style modifications along with patient information leaflet.

ACKNOWLEDGEMENT

The author likes to express his gratitude towards the Physicians of King George Hospital especially Cardiology department, King George Hospital and Avanthi Institute of Pharmaceutical Sciences for continuous support.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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