PAIN CONTROL IN SICKEL CELL ANAEMIA CRISIS: RETROSPECTIVE REVIEW OF IBUPROFEN AND PARACETAMOL USE.

Kethe Shravani[1*] Savanth Uthkarsha[1] Lakavath Kalyani[1] Erroju Vyshanvi[2] K.Purnachander[3] V.Rajkumar[4]

1.Department of Pharmacy Practice, Jyothishmathi Institute of Pharmaceutical sciences, Thimmapur, Karimnagar, Telangana, India.

2.Assistant Professor, Department of Pharmacy Practice, Jyothishmathi Institute of Pharmaceutical sciences, Thimmapur, Karimnagar, Telangana, India.

3. Associate Professor and HOD Jyothishmathi Institute of Pharmaceutical sciences, Thimmapur, Karimanagar, Telangana, India.

4. Professor and Principle, Jyothishmathi Institute of Pharmaceutical sciences, Thimmapur, Karimnagar, Telangana, India

*Corresponding author: Kethe Shravani

Department of Pharmacy Practice, Jyothishmathi Institute of Pharmaceutical sciences, Thimmapur, Karimnagar, Telangana, India.505481.

ABSTRACT:

Sickle cell disease (SCD) is a genetic disorder caused by mutations in the β-globin gene, leading to abnormal hemoglobin S and sickle-shaped red blood cells. It causes anaemia, vaso-occlusive crises, organ damage, and increased risk of stroke and infections. Diagnosis is confirmed by blood smear, hemoglobin electrophoresis, and genetic testing. Management includes hydroxyurea, novel therapies, pain control with NSAIDs or paracetamol, blood transfusions, and potentially curative stem cell or gene therapy. Early diagnosis and comprehensive care are crucial to reduce complications and improve quality of life.

KEY WORDS: Sickle cell anemia, Ibuprofen, Paracetamol, Blood Transfusion.

INTRODUCTION:

Sickle cell disease (SCD) is a genetic blood disorder caused by a mutation in the β-globin gene, resulting in the presence of hemoglobin S in red blood cells. This leads to abnormal molecular structure, sickling, anemia, vascular issues, and reduced oxygen transport.[1] The most severe type, hemoglobin SS (HbSS), affects 65% of people with sickle cell disease. It is caused by faulty hemoglobin gene alleles and causes organ damage, pain, and anemia.

A milder condition that affects 25% of patients is hemoglobin sickle cell anemia (HbSC). Inherited haemoglobin S and Haemoglobin D (HbSD), Inherited Haemoglobin S and Haemoglobin E (HbSE) and Inherited Haemoglobin S and Haemoglobin O- Arab (HbSO) are less common types that can lead to complications.[2]

EPIDEMIOLOGY :India has a very high rate of the S allele, which is linked to sickle cell anemia. This is especially true in Scheduled Tribe (ST) and Scheduled Caste (SC) communities. These groups make up about a quarter of India's total population. There are a number of reasons why the S allele is more common in these groups.

The S allele gives people who live in areas where malaria has been common a better chance of not getting sick. This heterozygote advantage keeps the allele in the population. Second, social and cultural practices like endogamy (marrying within the same group) limit genetic mixing, which raises the local frequency of the allele.[3]

ETIOLOGY:

There are two α-chains and two β-chains in hemoglobin (Hb). Point mutations in the gene that codes for the β-globin chain cause the differences between the common hemoglobin variants HbA, HbS, and HbC.

GENETIC FACTORS :

When a person inherits two defective sickle cell genes—one from each parent—sickle cell disease (SCD) results. Because of this, the body produces hemoglobin S, an aberrant form of hemoglobin that gives red blood cells a rigid, sickle- or crescent-shaped appearance. These sickled cells have the ability to obstruct blood flow, which can result in organ damage, anemia, exhaustion, infections, and pain episodes. SCD is a chronic illness that necessitates constant medical attention to control symptoms and avoid complications.[2] Patients experience painful "crises" caused by the obstruction of blood flow from sickled red blood cells.[3]

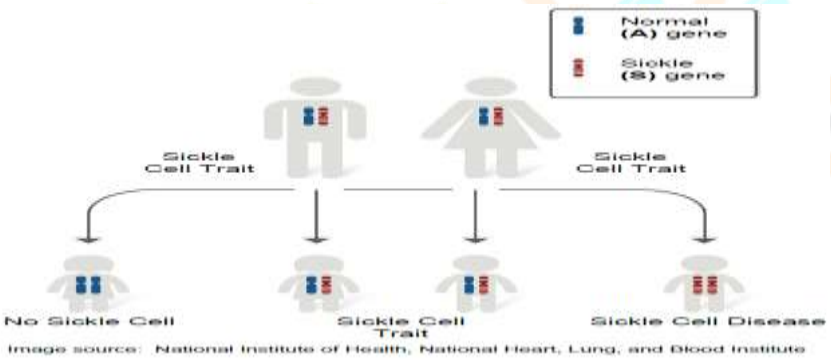

Figure 1: Chance of parents with SCT passing on to their children

SIGNS AND SYMPTOMS:

Sickle cell disease can lead to a variety of serious health complications. Anemia is a common symptom, causing fatigue, shortness of breath, and pale skin due to a reduced number of healthy red blood cells. Painful crises occur when sickle-shaped cells block blood flow, resulting in severe pain often felt in the chest, abdomen, joints, or bones. Another major complication is acute chest syndrome, a life-threatening condition caused by blockages in the lungs that lead to fever, chest pain, and difficulty breathing. Splenic sequestration may also occur when the spleen becomes filled with sickle cells, leading to severe anemia and potential spleen damage or removal. Additionally, sickle cells can obstruct blood vessels in the brain, particularly in children, increasing the risk of stroke. The rapid breakdown of sickle cells also releases bilirubin, which causes yellowing of the skin and eyes (jaundice).[4]

PATHOPHYSIOLOGY :

In sickle cell disease, sickled red blood cells block blood flow, causing pain and organ damage. These cells, along with plasma proteins and inflammatory cells, increase blood viscosity, worsening circulation and blockages. Haemolysis releases free heme and iron, leading to oxidative stress and inflammation that

activate the endothelium. Activated endothelial cells promote sickled cell adhesion and release pro-inflammatory chemicals, increasing tissue damage. Ischemia-reperfusion injury during brief blood flow restoration produces reactive oxygen species, further driving inflammation, oxidative damage, and disease progression.[6]

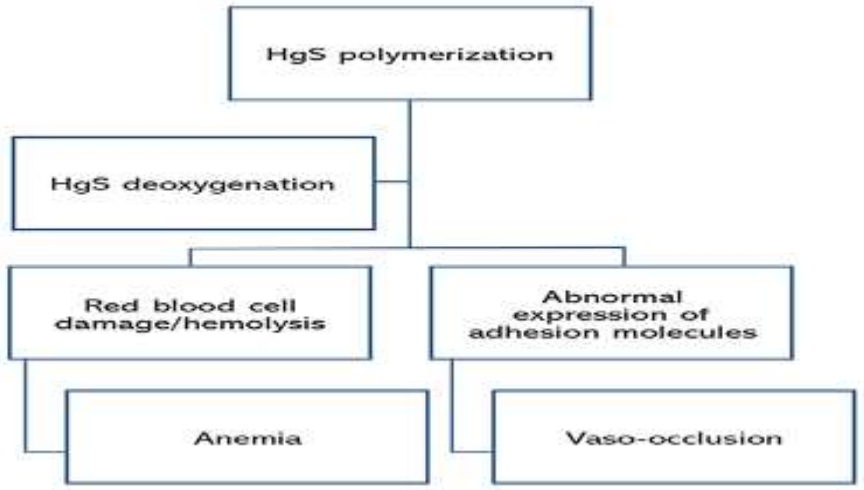

Figure 2: Pathophysiology of sickle cell anaemia [5]

RISK FACTORS:

Patients with sickle cell disease are at higher risk of severe complications if they have the HbSS or HbSβ⁰-thalassemia genotypes, lower fetal hemoglobin (HbF) levels, and higher steady-state hemoglobin or white blood cell counts. Additional risk factors include a history of asthma or atopy and exposure to tobacco, which increase susceptibility to pulmonary complications such as acute chest syndrome. These factors collectively contribute to more frequent vaso-occlusive events and worse disease outcomes.[6]

COMPLICATIONS:

Vaso-occlusive crises are the most common complication of sickle cell disease, causing severe pain when abnormally shaped red blood cells block blood vessels. This blockage reduces oxygen delivery to tissues, leading to pain in the bones, joints, abdomen, and chest. Episodes can be triggered by factors like dehydration, infection, or stress, and are usually managed with pain relief, hydration, and sometimes medications like hydroxyurea to reduce their frequency. The sickle-shaped red blood cells that obstruct blood flow in sickle cell disease can result in extensive complications. This frequently results in strokes in children, which cause irreversible brain damage and cognitive decline. The liver, kidneys, and other organs may sustain damage, malfunction, or be at higher risk of developing cancer. Because chronic anemia puts strain on the heart, it increases the risk of heart attacks, pulmonary hypertension, and heart failure. Damage to the retinal vessels may impair vision and result in blindness or detachment. If left untreated, priapism—painful, protracted erections caused by blocked blood flow—can also result in irreversible impotence.[3]

DIAGNOSIS:

Sickle-shaped red blood cells, which can be seen on a peripheral blood smear and occasionally appear microcytic, are a hallmark of sickle cell disease. The diagnosis is verified by hemoglobin electrophoresis,

which detects the aberrant hemoglobin S (HbS) and separates it from other variations or normal hemoglobin. By identifying the precise mutation in the HBB gene that causes sickle cell disease, genetic testing such as PCR or gene sequencing can provide conclusive confirmation and enable accurate diagnosis, carrier identification, and family counseling.[3]

TREATMENT:

Treatments for sickle cell disease (SCD) include both supportive and disease-modifying treatments. The first-line treatment Hydroxyurea raises fetal hemoglobin, which lowers the need for transfusions, painful crises, and acute chest syndrome. L-Glutamine helps patients 5 years of age and older experience fewer crises and hospitalizations. More recent therapies such as Crizanlizumab decrease crises by stopping sickle cells from sticking to blood vessels, and Voxelotor improve anemia by stabilizing hemoglobin. As part of supportive care, young children should receive prophylactic antibiotics to avoid serious infections as well as pain management with NSAIDs, opioids, and fluids. The combined goal of these treatments is to lessen complications and enhance the lives of those who have sickle cell disease.

Potential Curative Therapies:

Currently, the only known treatment for sickle cell disease is bone marrow or stem cell transplantation, which involves replacing the patient's bone marrow with healthy stem cells from a compatible donor. However, this procedure is extremely risky. Additionally, gene therapy is progressing; FDA-approved therapies such as Lyfgenia and Casgevy alter patients' own stem cells to produce fetal or normal hemoglobin. Although there is a considerable chance of both short-term and long-term adverse effects, blood transfusions are crucial for treating acute complications like stroke, acute chest syndrome, and organ failure.[7]

PAIN:

Pain episodes associated with sickle cell disease (SCD) are comparatively uncommon in neonates, infants, and young children (0–7.6 years), occurring on only 1.6% of days, with 14% of these episodes necessitating hospitalization. Infants under 12 months old are most commonly affected by dactylitis, which is characterized by painful swelling of the hands or feet. About 40% of children and adolescents aged 8 to 18 report episodic pain, and another 40% report chronic pain, making pain more common in this age group. Hospitalization, depression, and functional impairment are more common among those with chronic pain, even though both groups report comparable levels of pain and quality of life.[8]

IBUPROFEN:

Ibuprofen is a chiral 2-arylpropionic acid derivative NSAID[9]

Mechanism of action:

Ibuprofen is a non-selective COX-1 and COX-2 inhibitor with anti-inflammatory properties.[9]

Pharmacokinetics and Pharmacodynamics:

Ibuprofen has a half-life of roughly two hours, is quickly absorbed in both children and adults, binds to plasma proteins, and is mostly metabolized in the liver, where it is converted to hydroxylated or carboxylate derivatives that are subsequently eliminated by the kidneys. Pharmacodynamically, ibuprofen functions as a competitive, reversible inhibitor of COX-1 and COX-2 enzymes, lowering prostaglandin synthesis

momentarily while allowing enzyme activity to return after the medication is removed. This reversibility lessens the negative effects on organs such as the kidneys and stomach. Ibuprofen may also increase the production of endocannabinoids, which would add another way to relieve pain.[10]

Side Effects:

Dizziness, sleepiness, aseptic meningitis, platelet malfunction, and high blood pressure are all uncommon side effects[11]

PARACETAMOL:

The most widely used analgesic and antipyretic the world. It is listed among the essential medicines by the World Health Organization, which identifies the most effective, secure, and economical medications for priority illnesses[12]

MECHANISM OF ACTION

Paracetamol functions as a reducing co-substrate and blocks the COX site to inhibit prostaglandin synthesis, primarily in cells that are undamaged and have low levels of arachidonic acid. Additionally, it stimulates descending serotonergic pathways, and the use of 5-HT_3 receptor antagonists reduces its analgesic effects.[13]

Pharmacokinetics:

In the liver, paracetamol is primarily metabolized by glucuronidation and sulphation after being absorbed in the small intestine. A tiny quantity is also transformed into the toxic metabolite NAPQI, which is typically detoxified by glutathione. Genetic variability in CYP2D6, glutathione deficiency, and overdose can all raise the risk of toxicity. Due to slower metabolite elimination in patients with severe renal impairment, longer dosing intervals are necessary to prevent accumulation, and vulnerable groups such as the elderly, neonates, or malnourished people may need dose adjustments.[13]

Pharmacodynamics:

Paracetamol is grouped along with NSAIDs even though its own anti-inflammatory activity is rather minimal. The main reason for this is that the analgesic effect of paracetamol is thought to by exerted by COX enzyme

Side effects:

Allergic reactions

Flushing

Low blood pressure

Tachycardia

Blood disorders [13]

CONCLUSION :

Sickle cell disease (SCD) is a hereditary blood disorder caused by mutations in the β- globline gene, resulting in abnormal hemoglobin S that distorts red blood cells into a sickle shape. This leads to chronic hemolytic anemia, painful vaso-occlusive crises, organ damage, and increased risk of infections and stroke. The disease severity varies with genotype, with HbSS being the most severe. Management includes disease-modifying treatments like hydroxyurea, L-glutamine, crizanlizumab, and voxelotor, along with supportive care including pain control using NSAIDs such as ibuprofen and analgesics like paracetamol. Curative options like bone marrow transplantation and gene therapy are emerging but carry risks. Early diagnosis and comprehensive care are critical to reduce complications and improve quality of life.

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