Advanced International Journal for Research (AIJFR)
E-ISSN: 3048-7641 ● Website: www.aijfr.com ● Email: editor@aijfr.com

Sickle Cell Disease Revisited: Mechanisms, Literature Integration, And A Protocol for Crisis Care: An Integrative Review

Nicole Wafula[1], Prof. Nicholas Abinya[2]

[1]University of Nairobi
Level (V) Bachelor of Medicine and Bachelor of Surgery
Email: Nicolewafula1@gmail.com
[2]Master of Medicine in Internal Medicine from the University of Nairobi and completed a Fellowship in Medical Oncology at the Royal London Hospital (University of London) in 1992. Currently the Consultant Hematology-Oncologist at University of Nairobi.
Email: nicholasabinya@kesho-kenya.org

Abstract

Background

The most common cause of admission of sickle cell patients is Vaso-occlusive crisis which is the obstruction of vessels in the microcirculation by sickled cells. It is known that sickling of red blood cells happens when the patient is dehydrated and then they are exposed to hypoxic state. Despite this being a common clinical presentation of sickle cell patients, it has been noted that ta standard or a more evidence-based guideline on how to manage these patients to be an area that is still evolving and significant gaps persist making it inadequately defined with several aspects yet to be fully explored.

Methodology

This study is an integrative review that aims at explaining sickle cell disease from the basic intricate details to the pharmacological management of these patients. Therefore, there is a systemic review aspect which involves summarization of current published data explaining the pathophysiology of Vaso-occlusion, efficacy of intravenous fluid for hydration, pain management and toxins produced during ischemia as a result of VOC. A database search of PubMed, Wiley Cochrane, Scopus were performed. Of 5381 identified papers using the key search words a total of 28 studies which were a mixture of laboratory trials report, original research and systemic reviews were found eligible for the study. This research also involves original new data which consists of input from physicians obtained through a google form which aims at understanding their go to method of managing sickle cell patients, average stay of sickle cell patients in hospitals and what challenges they experience while managing sickle cell patients in a crisis.

Expected Outcomes and Significance

We anticipate to explain the mechanism behind Vaso-occlusive crisis and how pharmacologic management from the intravenous fluid administration and pain killers use can be guided by the mechanisms behind

the VOC. We also anticipate to clarify why some of the currently used methods might be detrimental especially in management of sickle cell patients.

Protocol

This research also involves the introduction of basic protocol schematic that can help guide physicians when dealing with sickle cell patients while drawing reference from a paper written by John Hopkins All Children's Hospital guideline but using conditions that are mostly seen in Kenya.

Conclusion

In conclusion, some of the currently used management strategies of VOC are dangerous such as use of 0.9% normal saline in IV fluid hydration which has been proved to even worsen the cell sickling while an alternative is being proposed more likely a fluid with an osmolarity of (111-122) mEq/L. The promising use of intravenous acetaminophen rather than NSAIDS might be more useful in managing the pain.

1. Introduction

Sickle cell is an inherited autosomal recessive hemoglobinopathy characterized by polymerization of hemoglobin S upon deoxygenation that results in the formation of rigid sickled shaped red blood cells which can occlude microvasculature, which leads to sudden onsets of pain. It is a group of diseases which are: sickle cell anemia (HbSS), sickle hemoglobin C (HbSC), Sickle beta plus thalassemia (HbS β^{+}) and sickle beta zero thalassemia. Sickle cell anemia being the most severe and one which is most common in Kenya the area of this study's focus.

Red blood cells contain hemoglobin which is protein in charge of transporting oxygen. A non-sickle cell patient has a hemoglobin which is a tetramer of 2 alpha and 2 beta chains. However, in sickle cell disease a group of monogenic disorders characterized by defects in the beta hemoglobin subunit due to mutations in the hemoglobin beta gene on chromosome 11. Given that healthy red blood cells are round, hence the ability to move through small blood vessels to deliver oxygen to all parts of the body. In Sickle cell disease the hemoglobin is abnormal, making them to become hard and sticky and often die which causes shortage of red blood cells.

In small blood vessels they get stuck and obstruct blood flow what is often referred to as Vaso occlusive crisis. Vasoocclussive crisis is the leading cause of hospitalization in sickle cell disease. As these patients will often present to health care facilities with complaints of; PAIN! (even in unexpected areas like fingers), chest pain/shortness of breath, abdominal pain, headache/neurological changes, penile pain/priapism, limb pain.

Children with sickle cell disease start to have symptoms during their first year of life at around 5 months of age when the fetal hemoglobin wears off and the sickle cell disease hemoglobin effects kicks in.

It is estimated that each year over 300,000 children are born annually with the disease and over 70% of these births occur in sub-Saharan Africa. In Kenya, it is estimated that 14,000 children are born with sickle cell disease annually with a particular area of focus being the county of Kisumu where in every 100 children 21 of them are born with sickle cell disease. This is because the area is a lake region and the cases

of Malaria were and still are rampant in this region. The body developed the sickle cell gene as a protective mechanism against malaria infection.

Sickle cell disease is a significant contributor of non-communicable disease related child mortality globally causing 6-15% in children less than 5 years. In Kenya, 50-90% of those born with the condition die before their fifth birthday due to sepsis and crisis.

1.1 Research Question

How do current clinical practices and physician preferences in fluid management and analgesics use align with emerging protocols and literature in the comprehensive care of patients with sickle cell disease and is it possible to introduce a new protocol of management for these patients which will enable faster alleviation of pain, shortened hospital stay and less post-crisis complications?

1.2 Background

Despite the burden that this condition causes, it remains highly unresearched and protocols on how to manage it remains unclear. This research aims at understanding the disease from its basics to its core intricate details with an aim of using this information to make an informed and justified protocol on how to manage these patients so as to alleviate pain, improve quality of life and if possible, alleviate or even eradicate mortality which trace back to SCD being the cause of death.

In order to attain this goal, this research is an integrative review meaning that it contains both systemic review and meta-analysis as well as newly collected data. This is to enable the understanding from what is known to what is unknown. The systemic and meta-analysis section involves comprehensive analysis of already published data while the newly collected data is information concerning doctors current understanding and preferences of pharmacologic approach in management of sickle cell patients to application of the suggested protocols.

1.3 Hypothesis

This research suggests that the current clinical protocols and physician understanding/preference for fluid balance and analgesia use in sickle cell disease especially in Vaso occlusive crisis do not fully align with pharmacologic evidence revealing a gap between pathophysiologic understanding and practical strategies and therefore a review of the pathophysiology of sickle cell pain and a guide on multimodal analgesia with proper fluid administration may improve the patients' management.

1.4 Significance of the research

This research addresses the approach of decentralizing opioid monotherapy, emphasizes on the need of addressing the VOC pain from multiple perspectives, giving a protocol of dealing with crisis pain in our set-up and addressing physician claims and barriers while at it.

2. Literature Review

2.1 Understanding the sickle cell disease and vaso-occlsuion

Sickle cell disease is a hemoglobinopathy that is caused by monogenic substitution of a single amino acid on the beta chain which is (adenine to thymine), this unique hemoglobin that is formed is the sickle cell hemoglobin. The evolutionary understanding is that this mutation happened in order to reduce the malaria infection. Malaria is an in infection that is transmitted by the female anopheles' mosquitos and it often

thrives in high oxygen environments which in sickle cell disease the hemoglobin has less oxygen carrying capacity. This therefore explains the localization of SCD among people of specific origin. During dehydration, the concentration of hemoglobin S increases in the red blood cells. Given that the individual is exposed to reduced oxygen situations, the increased tonicity of hemoglobin s in the red blood cells polymerizes which results in deformation of the RBC and this makes them rigid and unable to easily pass through small capillaries. Therefore, they clog the microcirculation causing pain. Normally, these cells can reverse their sickling upon exposure to proper oxygen and rehydration however multiple deoxygenation/reoxygenation causes irreversible sickling. The vasooclusion and polymerization eventually results in chronic hemolysis.

Intravascular hemolysis and release of free hemoglobin leading to nitric oxide depletion, endothelial dysfunction and neutrophil and platelet adhesion are all playing an important contributory role in the pathophysiology of SCD.

This therefore explains the idea behind the novel invention of hydroxyurea which is aimed at increasing the amount of fetal hemoglobin hence reducing the concentration of hemoglobin S in the RBCs and therefore reducing the episodes of RBC sickling upon dehydration and deoxygenation.

The pathophysiology of vaso-occlusion is based on two concepts which are delay time and transit time. Delay time refers to the time it takes for the red blood cell to become deoxygenated while in the microvasculature to the time the hemoglobin in it polymerizes. Transit time refers to when the regional blood flow decreases and therefore the time it takes for the red blood cells to pass through is prolonged. Therefore, an understanding on how to solve vaso-occlusion is by prolonging the delay time while reducing the transmit time.

Therefore, in a case of Vaso-occlusion there is increased hemolysis which introduces a new concept of increased oxidative stress, depletion of nitric oxide, increase in E and P selectins and increased plasma potassium levels.

Current literature emphasis intravenous fluid administration is the usual practice during VOC episodes to slow the sickling process however there is no clear guideline on how much fluid administration is safe to administer without causing fluid overload. These same literatures advocate for use of normal saline as the mainstay fluid in IVF.

The literature also advocates for use of opioid monotherapy as the main stay treatment.

2.2 Gaps identified

1.Pharmacokinetic translation- There is need for understanding the importance of rehydration of sickle cell disease patients before administering intravenous paracetamol and this will help explain the risk of suboptimal dosing and pain control.

2. Protocol variability- Fluid and analgesic protocols differ across institutions and regions. The fluids recommended for IVF have adverse effects and even possibly worsening the crisis therefore explaining why there is inconsistent patient outcomes and clinician uncertainty.

3. Physician knowledge – there is limited integration of pharmacologic evidence into clinical decision making hence explaining why there is missed opportunities for personalized care and less monitoring of the advanced reactions of patients to the administered management.

3. Research Objectives

The research broadly aims at explaining the sickle cell disease based off all the published literature so as to enable understanding of its pathophysiology which will guide the choice of pharmacologic management with an attempt of improving patient management which in the long run will possibly reduce the hospital stay and accelerate pain alleviation.

3.1 Broader objectives

1.Understand the pathophysiology of Vaso-occlusion

2.Understand the physicians understanding on management of SCD crisis from fluid administration to analgesics used.

3. Understand new published research that contraindicate the current practice.

4. Develop a protocol on how to deal with SCD crisis in our setting based off documented literature as justification

3.2 Specific objectives

1.Understand the specific mechanisms at which some of the currently used management strategies are contributory to crisis worsening.

2. Understand the mechanism of action in intricate details on how the suggested new management therapies will assist in better management of sickle cell patients.

3. Suggest the multi-disciplinary approach in management of sickle cell patients.

4. Research Methodology

(A). SYSTEMATIC REVIEW AND META ANALYSES

The preferred reporting items for systematic reviews and meta-analyses PRISMA guideline was adopted for this study

4.1 Search strategy

A comprehensive search of PubMed, Wiley Cochrane Library, Clinicaltrials.gov and Embase databases were performed to identify relevant articles from database inception until 24th September 2025. The following terms in their specific criteria of issue addressed were used:

TABLE 1: TABLE ON CRITERIA AND KEY WORDS

CRITERIA	KEYWORDS
1.VASOOCCLUSION	1.sickle cell AND Vaso-occlusive
2.HYPERKALEMIA	1.sickle cell AND hyperkalemia
3.MYOGLOBIN	1.Myoglobin AND infarction
4.FLUID ADMNSTRATION	1.sickle cell AND intravenous fluid 2.sickle cell AND fluid overload 3.sickle cell AND saline
5.PAIN MANAGEMENT	1.sickle cell AND emergency 2.sickle cell AND pain 3.sickle cell AND pain killers 4.sickl cell AND opioids
6.MORTALITY	1.sickle cell AND death 2.sickle cell AND mortality 3.sickle cell AND autopsy

Search was expanded by using vague terms such as "sickle cell" in the search strategy to identify more potentially relevant articles. The citations within the studies were assessed for other potentially suitable studies.

4.2 Eligibility criteria

Types of studies

The studies included in this systematic review encompass a diverse range of methodologies, including retrospective and prospective analyses, laboratory based experimental designs, and previously published systematic reviews.

Types of participants

All SCD patients who were taken to the accident and emergency, casualty or generally hospitalized.

Exclusion criteria

Studies with a quality score of 6 or less on the modified New-castle Ottawa scale or studies that lacked sufficient data on the above-mentioned criteria were excluded. Studies that discussed any condition that is not specifically sickle cell disease were also excluded.

4.3 Study screening, selection and data extraction

Potentially suitable studies were evaluated and any uncertainties were discussed with the supervisor of the study. The titles and abstracts of the search results were screened for eligibility followed by removal of duplicate studies. All potentially suitable studies underwent full text review to assess eligibility. Eligible studies were included in this review. Data were extracted. The information, when available was extracted from the studies: author, year of publication, type of study.

4.4 Quality assessment and data synthesis

All included studies were critically appraised for methodological quality. Data analysis was conducted using a narrative approach for narrative oriented studies while meta-analysis was done for certain studies.

4.5 Results

Table 2: Table On Criteria, Key Words and Number of Papers

CRITERIA	KEYWORDS	NUMBER OF PAPERS
1.VASOOCCLUSION	1.sickle cell AND Vaso-occlusive	238 papers 3 fitting the criteria 0 duplicates Total= 3 papers
2.HYPERKALEMIA	1.sickle cell AND hyperkalemia	43 papers 6 fitting the criteria 0 duplicates Total = 6 papers
3.MYOGLOBIN	1.Myoglobin AND infarction	1 paper
4.FLUID ADMNSTRATION	1.sickle cell AND intravenous fluid 2.sickle cell AND fluid overload 3.sickle cell AND saline	5099 papers 6 fit the criteria 0 duplicates Total=6 papers
5.PAIN MANAGEMENT	1.sickle cell AND emergency 2.sickle cell AND pain 3.sickle cell AND pain killers 4.sickl cell AND opioids	1066 papers 11 fitting the criteria 0 duplicates Total= 11 duplicates
6.MORTALITY	1.sickle cell AND death 2.sickle cell AND mortality 3.sickle cell AND autopsy	4849 papers 1 fit the criteria 0 duplicates Total=1 paper

4.5.1 VASOCCLUSION

This criterion is specifically aimed at explaining the mechanism of Vaso-occlusion in sickle cell patients. Out of the 238 papers that fit the key word criteria, 3 papers with zero duplicates were found to provide insightful explanations which will be suitable in this study when it comes to understanding the best mechanism of managing sickle cell patients in Vaso-occlusive painful crisis. The three papers are entitled:

- The physical foundation of Vaso-occlusion in sickle cell disease
- Simultaneous polymerization and adhesion under hypoxia in sickle cell disease
- Vaso-occlusion in sickle cell disease; is an autonomic dysregulation of the microvasculature the trigger?

The first Paper aimed at explaining the biomechanical pressure needed to dislodge a single sickled red blood cell from the capillary sized constriction and relating that to in vivo pressures in microcirculation. Testing was done on capillaries while occlusion in SCD often happens in post-capillary venules which happen to be larger than micro vessels. This was tested on microfluidic channels which mimic capillary geometry and the testing was dependent on intracellular hemoglobin concentration. It was discovered that the maximum pressure that was required to dislodge a sickled cell from a capillary was about 100 pascals which is much smaller than typical pressures in the microcirculation pressures which range between 0.7Kpa to 7.9Kpa (depending on the tissue). Dislodging pressures increase with the concentration of hemoglobin S in the cells. In conclusion, an increase in the intravascular volume and a decrease in hemoglobin S concentration results in an increased delay time.

The second paper, aimed at investigating simultaneously how Hemoglobin S polymerization and red blood cell adhesion interact under low oxygen conditions in SCD and also how maturity influences this coupling. Samples of 8 SCD used proved that hypoxia is a strong initiation of adhesion while young reticulocytes are also a strong initiator of adhesion while low. This adds a novel discovery suggested that patients with an increased reticulocyte count are more likely to have multiple episodes of VOC. The trigger for high reticulocyte count is increased hemolysis. Therefore, it is in fact necessary to keep the hemolysis of SCD patients on check to avoid multiple episodes of VOC.

The third paper strived at explaining the concept of delay time and transit time model as a core determinant of Vaso-occlusive crisis.

4.5.2 HYPERKALEMIA

This section is specifically aimed at understanding the incidence of hyperkalemia that is often an under-looked concern during a crisis and has been proved to be a contributory factor in SCD related deaths. Using the key search words, 43 papers showed up and only 6 of them with zero duplicates fit the criteria.

From the 6 papers it is necessary to note that hyperkalemia and acid base balance in sickle cell disease patients is vital in their management and is often attributed to three integral domains: renal function, electrolyte balance and gastrointestinal tract integrity. Of note is that even in steady state (not in crisis) SCD patients often display hyperkalemia which could be due to ongoing hemolysis, microvascular ischemia (which resolve before becoming a crisis) as drug related complications. However, it is necessary to note that the hyperkalemia becomes more prominent during a crisis and even after emergency treatment in hospital.

In a study in Netherlands on a study population of 83 people, it was proved that hyponatremia and hyperkalemia being more prominent in SCD patients than non SCD patients with no comorbidities. In the study done at Makerere University proved that SCD patients tend to develop hyperkalemia and metabolic acidosis much earlier at GFR values which are considered normal in general populations with a strong correlation between hemolysis (increased LDH) and hyperkalemia.

It is also necessary to note that patients often present with increasing levels of hyperkalemia even after admission at the hospital and while undergoing management for the crisis. These patients are often managed with NSAIDS which are known to be contributory to the hyperkalemia.

4.5.3 MYOGLOBIN

The one paper in this section is entitled "Myoglobin release after tourniquet ischemia" it is aimed at explaining myoglobin into the blood stream after periods of ischemia. Despite this not being directly linked to SCD. It is necessary to understand that myoglobin is one of the contents released during a Vaso-occlusive crisis and due to its nephrotoxic properties, it may be playing a vital role in sickle cell nephrology. The necessary findings in these papers are that there is a timeline of myoglobin release.

- Pre-release- which is myoglobin contained within muscle cell.
- Post-release- as blood flow returns myoglobin begins to enter the circulation
- Peak concentration- myoglobin levels in the plasma reach their maximum 8-10 hours after tourniquet release
- Gradual decrease- Myoglobin levels gradually decrease over the next 50-60 hours returning to pre tourniquet levels.

4.5.4 FLUID ADMNISTRATION

While using the key words for the search, a total of 5099 papers result was achieved. However, upon farther evaluation only 6 of these papers with 0 duplications fit the criteria. Upon further evaluation only 2 of these papers addressed the needs of this paper. A paper entitled "Commonly used clinical intravenous fluid formulations differently affect sickle red blood cells stiffness and transit time" Washed red blood cells diluted to low hematocrit (0.5%) and exposed to different intravenous fluid formulations (normal saline, D5) and use of microfluidic devices to measure transit time of single red blood cells through narrow channels. It was discovered that 0.9% normal saline increases red blood cell stiffness and prolongs transit times through micro channels, hypotonic fluids increase mean corpuscular volume and subsequently reduced intracellular hemoglobin s concentration and although hypotonic conditions decrease adhesions the overhydrated cells transit slowly. Intermediate fluids with moderate sodium levels (111-122mEq/L) result in better RBC deformability and shorter transit time with lower occlusion risk while also decreasing intracellular hemoglobin S concentration.

The second paper entitled "Fluid overload due to intravenous fluid therapy for Vaso-occlusive crisis in sickle cell disease incidence and risk factor" This retrospective cohort study with 100 SCD patients with median age of 25 years showed that 21% of patients developed fluid overload during intravenous management for Vaso-occlusive crisis. Fluid overload may complicate acute chest syndrome causing pulmonary oedema, peripheral oedema, weight gain and increased need for oxygen. Fluid overload is common affecting 1 in 5 SCD patients during treatment of VOC with IV fluids. It is also mentioned that 0.9% normal saline which has high chloride load can cause metabolic acidosis which may worsen sickling. In conclusion, the safe amount of fluid administration is 3L/24 hours at an optimum temperature of 37.5degrees.

4.5.5 PAIN MANAGEMENT

While using the key search words, a total of 1066 papers were found but out of these only 11 with 0 duplicates fit the criteria of the context of this paper. The summary of the papers is in the form of a table as below:

Table 3: Table On Studies On Pain Killers and Ulcers

STUDY	POPULATION	ULCEER PREVALENCE	NSAID/Ibuprofen link
Akere et al 1989 Nigeria, endoscopy	51Hbss patients with recurrent epigastric pain	18/51(35%) had duodenal ulcers and the rest had gastric ulcers	NSAID use not systematically reported but the mentioned analgesic use in SCD patients
Hariharan et al Blood advances 2020 California cohort	6423 SCD patients	Among upper Gastrointestinal bleeds 10% were due to PUD	NSAID is a plausible risk factor in SCD gastrointestinal bleeds
Case report	Individual SCD patients	Severe gastric bleeding occasionally life threatening	Direct temporal link to Ibuprofen or other NSAIDs

Mild Pain

- Acetaminophen (paracetamol) ± NSAID (e.g., ibuprofen, diclofenac, ketorolac).
- Avoid long-term NSAID in renal disease.

Moderate Pain

- Oral opioid (e.g., codeine, tramadol, or oral morphine) + continue non-opioid (paracetamol/NSAID).
- Monitor for escalation.

Severe Pain (typical VOC crisis)

- Strong opioid (parenteral preferred)
  - Morphine IV
  - Hydromorphone IV
  - Fentanyl IV/patch (alternative if morphine intolerance).
- PCA (Patient-Controlled Analgesia) recommended where available.
- Continue acetaminophen ± NSAID if renal function allows.
- Consider adjuvants:
  - Ketamine (low-dose infusion) for refractory pain or opioid tolerance.
  - Gabapentin/amitriptyline for neuropathic components.

See table 3on: GASTRIC AND DUODENAL ULCERS IN SCD

4.5.6 MORTALITY

In this section, we explore autopsies of SCD patients and using this published data to make justified corrections on how to manage these patients better. It is documented that majority of SCD patients who succumbed while being hospitalized in hospital suffered pulmonary oedema which is secondary to fluid

overload. Their average duration of hospital stay was about 4 days with (P=0.037) this resulted in overall increased demand for oxygen The retrospective review of autopsy studies on 21 SCD patients proved this common pathologic finding accounting 48% of the patients. This is documented in a paper entitled "Fluid overload due to intravenous fluid therapy for Vaso-occlusive crisis in sickle cell disease incidence and risk factor"

Additional studies have shown hemorrhagic peptic ulcer disease due to intake of NSAIDS among sickle cell patients to be among the leading cause of death among SCD patients.

(B). NEWELY COLLECTED DATA IN THIS STUDY

4.5.7 PHYSCIAN UNDERSTANDING ON MANAGEMENT OF SCD PATIENTS

A google form was circulated among medical doctors who have been practicing for more than a year and input was gathered on:

1. They preferences based on their experience on how to manage SCD patients who are undergoing a crisis
2. How long SCD patients to stay in the hospital
3. What challenges they tend to encounter
4. What they would love to be changed concerning management of SCD patients.

PREFRENCES

Majority of the physicians prefer intravenous fluid hydration using 0.9% normal saline, intramuscular opioid pain killer especially morphine, intravenous antibiotic and monitoring.

It is necessary to note that the IVF fluid administration is regulated by the pain when the pain decreases, they reduce the amount of fluid administered when the pain increases both fluid and pain killer administration increases with no specific limit and attention to temperature of the fluids.

HOSPITAL STAY

Majority of the answers ranged between 5-10 days.

CHALLENGES

1. Lack of co-operation from the blood transfusion department
2. Getting a proper history to the patient who is in pain
3. Lack of awareness on genetic testing
4. Lack of compliance to the medication by the patients
5. Abuse of opioids and addiction
6. Administration of antibiotics to SCD patients who do not need them.

CHANGES THEY WOULD LIKE TO SEE

1. Clinical officers to be guided on how to properly manage a sickle cell patient.

5. Discussion

Sickle cell disease affects millions of people around the world and in Kenya it holds a great percentage in the non-communicable diseases. Directing the interest to Kisumu County where approximately 21 out of 100 children are born with the condition. 50-90% of these children do not live beyond their fifth birthday while those who live have to endure a lifetime of painful vaso-occlusibve crisis of which little is known about its proper management. It is necessary to understand that timing and understanding of the root cause of the crisis as well as an understanding of the pathophysiology of Vaso-occlusive crisis remains the most important trimodal when it comes to management of a patient in crisis.

It is understood that when the intracellular concentration of hemoglobin S is high, especially during times of dehydration and then subjected to hypoxia, the hemoglobin S polymerizes making the RBC rigid and less deformable hence it can easily get stuck in microcirculation. If we implement the model of delay time, it is necessary to understand that if these cells are hydrated but not too hydrated then we can reduce the concentration of hemoglobin S hence allowing reversible sickling while also increasing the intravascular volume to increase the pressures to dislodge the sickled cells as we have already stated in this paper that pressures as little as 100 pascals can dislodge the RBC. It is of concern that majority of medical textbooks, online resources and real -life practice has normalized the use of 0.9% normal saline as the main stay fluid for intravenous fluid resuscitation. However, in this paper we have shown that 0.9% normal saline is in fact more detrimental because it has an osmolarity of 308mOsm/L which is higher than 290mOsm/L and even more acidic than the plasma at Ph of 5.6. This triggers more drainage of fluid from the RBCs hence the concentration of hemoglobin S increases resulting in more rigid cells. In a study that was done, it was concluded that fluid at 111-122mEq/L is the most suitable in crisis management. Hatch et al in 1965 suggests vigorous IVF hydration, while another study by Guy et al in 1971 suggested that an infusion of a large volume of hypotonic fluid can induce hyponatremia. In this study we chose to merge these three findings by suggesting the use of either:

(i). 115mEq/L Normal saline which is most likely created by mixing half normal saline (0.45%normal saline – 77mEq/L) with standard normal saline (0.9% normal saline- 154mEq/L) in different ratios to yield intermediate sodium concentrations.

1part standard NS+ 1 part half normal saline= 115mEq/L

Despite this not being a standard fluid, it can be ordered or prepared for the sake of sickle cell patients management.

(ii). D5 0.45%Normal saline (D5 And half normal saline)

This is an intravenous fluid that combines dextrose and hypotonic saline.

Dextrose (D5) 5%= 50g/L

Sodium chloride (NaCl) 0.45%= 77mEq/L sodium + 77mEq/L chloride

In the body the dextrose (sugar) is rapidly metabolized by cells a process which requires the Prescence of insulin for it to take place. Since we have already established that there is hyperkalemia in SCD patients even in steady state but it can become even more pronounced during a crisis and that potassium is a potent activator of nociceptors. The insulin will facilitate the intracellular intake of the excess potassium. This

entire process leaves behind only 0.45% normal saline which hypotonic that will result in cellular hydration while avoiding the problem of hyponatremia.

It is necessary to ensure a maximum of 3L/24 hours of fluid intravenous administration for adults to avoid fluid overload which was well documented by Gaut et al ho who suggested that fluid overload has a potential link to acute chest syndrome which will manifest clinically as pulmonary edema. It is also necessary to consider the IVF should be at 37.5 degrees as this has been linked to a faster recovery.

Pain management remains a priority in management of sickle cell patients as their pain has been described to be excruciating. From the PHEDRE trial, it was noted that opioid monotherapy has been linked to addiction and not as efficient in pain management and therefore a multimodal approach is considered more effective. Despite NSAIDS being linked to levels of efficiency it is necessary to note that it is never a one size fits all as NSAIDS have been associated with mortality of SCD patients due to peptic ulcer disease and acute kidney injury a study well documented by Bddam et al. NSAIDS also contributes to hyperkalemia. Therefore, the preferred pain management is intravenous paracetamol after hydration which is to enable adequate volume of distribution for the analgesic with a combination of a slow releasing intramuscular opioid like tramadol once administration of the intravenous paracetamol ends re-instate the intravenous hydration fluid while monitoring the patient's fluid chart (input and output). This is to ensure proper distribution so as to avoid acetaminophen poisoning. It is however necessary to confirm the patient's liver function test results before administering some medications like tramadol and that is laboratory investigations is important in the initial workup of these patients.

In pregnant SCD patients, recent meta-analysis has proved that prophylactic transfusion programs in pregnancy are associated with fewer VOCs, fewer pulmonary complications and improved maternal/fetal outcomes in many cohorts.

Pethidine should be avoided due to its neurotoxicity while NSAIDs avoided after 30-32 weeks unless benefits outweigh risks. Patients should be advised to avoid triggers while paracetamol is recommended when needed.

1. Assessment

- Use validated pain scoring tools (VAS, FLACC, Wong-Baker Faces).
- Evaluate pain type (acute VOC nociceptive vs neuropathic vs chronic pain).
- Document baseline opioid requirements if patient has history.

2. Pharmacologic Management

Mild Pain

- Acetaminophen (paracetamol) ± NSAID (e.g., ibuprofen, diclofenac, ketorolac).
- Avoid long-term NSAID in renal disease.

Moderate Pain

- Oral opioid (e.g., codeine, tramadol, or oral morphine) + continue non-opioid (paracetamol/NSAID).
- Monitor for escalation.

Severe Pain (typical VOC crisis)

- Strong opioid (parenteral preferred)
  - Morphine IV
  - Hydromorphone IV
  - Fentanyl IV/patch (alternative if morphine intolerance).
- PCA (Patient-Controlled Analgesia) recommended where available.
- Continue acetaminophen ± NSAID if renal function allows.
- Consider adjuvants:
  - Ketamine (low-dose infusion) for refractory pain or opioid tolerance.
  - Gabapentin/amitriptyline for neuropathic components.

3. Non-pharmacologic Adjuncts

- Hydration (avoid excessive fluid overload, use isotonic solutions cautiously).
- Heat, massage, relaxation techniques.
- Cognitive Behavioral Therapy (CBT) for chronic/recurrent pain.

6. Basic Protocols

MANAGEMENT OF SICKLE CELL PATIENTS

6.1 General Flow During Patient Encounter

1. Patient with a history if sickle cell disease presents at the health facility
2. Check if the patient has a fever
   - If fever is present- Kindly consider the possibility of an infection by getting cultures done and antibiotic treatment should be administered after necessary laboratory confirmation tests like (FBC, cultures and CRP)
   - If there is no fever – proceed with this pathway
3. Initial management of the patient
   - Start an Intravenous line
   - Draw blood for laboratory investigations. (Full blood count, Liver functioning tests, Urea electrolyte and creatinine)
4. Hydrate the patient using intravenous fluid solution that are recommended in this study.
5. PAIN MEDICATION!

Mild Pain

- Acetaminophen (paracetamol) ± NSAID (e.g., ibuprofen, diclofenac, ketorolac).
- Avoid long-term NSAID in renal disease.

Moderate Pain

- Oral opioid (e.g., codeine, tramadol, or oral morphine) + continue non-opioid (paracetamol/NSAID).
- Monitor for escalation.

Severe Pain (typical VOC crisis)

- Strong opioid (parenteral preferred)
  - Morphine IV
  - Hydromorphone IV
  - Fentanyl IV/patch (alternative if morphine intolerance).
- PCA (Patient-Controlled Analgesia) recommended where available.
- Continue acetaminophen ± NSAID if renal function allows.
- Consider adjuvants:
  - Ketamine (low-dose infusion) for refractory pain or opioid tolerance.
  - Gabapentin/amitriptyline for neuropathic components.

6. Investigate on what is the cause of the crisis:
   PENILE PAIN
   1. Sickle cell disease priapism
   2. Urinary tract infection
   3. Sexually transmitted infection

   NEURO-CHANGES

   1. Sickle cell disease stroke
   2. Headache
   3. Sepsis

   ABDOMINAL PAIN

   1. Sickle cell disease cholecystitis
   2. Sepsis
   3. Constipation
   4. Sickle cell disease splenic sequestration

CHEST PAIN

1.Acute chest syndrome

2.Pulmonary embolus

3.Sepsis

6.2 Sickle Cell Aplastic Crisis Management
SIGNS AND SYMPTOMS

1. Symptomatic anemia (Fatigue, shortness of breath, palpitations and headache).
2. Abdominal pain and vomiting
3. Fever and jaundice
4. Decreased hemoglobin by >=2g/dl from the patient's regular baseline (+/- thrombocytopenia/leukopenia) without appropriate reticulocyte count
   WORKUP AND MANAGEMENT
5. 1.Start IV, FBC, Reticulocyte, blood type testing

6. 2. Microbiology panel: Human parvovirus B19, Mycobacterium tuberculosis, Salmonella typhi, Brucella, Human immunodeficiency virus, Malaria
7. 3.Hydrate and administer pain management
8. 4. Transfuse to goal of 8-9g/Dl
9. 5.Discharge home when clinically stable and not in pain with close follow up

6.3 Sickle Cell Disease Cholelithiasis/Cholecystitis Mangement

GALL BLADDER DISEASE

Suspected with RUQ pain (+/- fever for cholecystitis), intolerance of per oral/ vomiting especially fatty foods or post-prandial pain, jaundice/icterus

Positive murphy's sign upon examination

1. Labs: FBC, reticulocytes, LFT (esp. GGT), amylase, lipase, blood type.
2. IVF bolus
3. IV pain medication
4. IV ondansetron for the vomiting
5. RUQ ultrasound
6. If febrile, obtain blood cultures, start IV ceftriaxone 50mg/kg

6.4 Sickle Cell Disease Priapism Management

Priapism is defined as suspected with sustained erection for more than 2 hours or painful erection lasting any duration of time.

- History of the patient should be obtained for: WHAT TIME THE PRIAPISM STARTED BECAUSE IT SHOULD BE TREATED AS AN EMERGENCY! Use of medications, infections and trauma.
- Start an intravenous line, obtain blood for laboratory tests (FBC, LFTs, UEC, blood type).
- Consult the hematologist and urologists

If the Priapism has been present for less than 4 hours then:

- Therapeutic decompression of corpora cavernosa
- Intravenous fluid hydration
- Pain management intravenous paracetamol
- Oral pseudoephedrine

If the priapism has been present for more than 4 hours then:

- Intravenous fluid hydration
- Pain management intravenous paracetamol
- If hemoglobin is less than 9g/Dl consider transfusion
- Urology consultation

6.5 Medications to Be Avoided in Sickle Cell Disease Due to Their Hyperkalemia Effect

1. Angiotensin converting enzyme inhibitors- Enalapril
2. Angiotensin (ii) receptor blockers- Losartan

3. Potassium sparing diuretics- Spironolactone
4. NSAIDs- Ibuprofen
5. Heparin

The use of these medications can be justified if the patient is an absolute need of them.

7. Conclusion

Sickle cell disease remains one of the leading contributing diseases in the bracket of non-communicable diseases in Kenya. Considering that many people live with this condition, it is necessary that evidence-based guidelines on how to manage these patients is implemented. In this study, we delved into understanding the pathophysiology of Vaso-occlusion crisis and using this information to integrate pharmacotherapy approach to effectively manage these patients while at the same time avoiding adverse effects that may emerge from an inappropriate administration of there management while using published literature on autopsy findings of sickle cell disease patients such as pulmonary oedema as a result of fluid overload. This study suggests the use of hypotonic intravenous fluid of (111-122mEq/L) at 37.5 degrees with a maximum of 3L/24hours, multimodal pain killers with more affiliation for intravenous paracetamol while emphasizing the need of careful use of non-steroidal anti-inflammatory medications. The paper also contains input from physicians to understand their understanding on management of sickle cell crisis and what they would like to be changed about the process.

Acknowledgment Section

I would like to thank my Mentor and lecturer Professor Nicholas Abinya for his continued support and guidance in the understanding of sickle cell and his advice on how to approach the research question. I would also like to thank my mother (Janet Nyabinge) for her moral support during the entire process of writing this paper as well as my two sisters (Winnie and Mitchelle Wafula). Last but not least I would like to thank my friends for their motivation while writing this paper (Nicholas. K, Misaki.K, Rachit.V, Atemel.I and Ben.O). The above-mentioned people have given consent for their names to be included in this paper.

I would also like to thank the doctors who advised me on the challenges they tend to experience while managing sickle cell disease through a google form which I had access to and giving me consent to use that information to guide the trajectory of this paper. There is no granting or any form of funding that has been granted to the writing of this paper.

References

1. **Aluoch, J. R.** (1989). Renal and electrolyte profile in steady state sickle cell disease: Observations in patients with sickle cell disease in The Netherlands. **Tropical and Geographical Medicine**, **41**(2), 128–132. PubMed ID: 2763358
2. **Saraf, S. L., Derebail, V. K., Zhang, X., Machado, R. F., Gordeuk, V. R., Lash, J. P., & Little, J.** (2022). Hyperkalemia and metabolic acidosis occur at a higher eGFR in sickle cell disease. Kidney360, 3(4), 608–614. https://doi.org/10.34067/kid.0006802021

3. **Gaut et al. (2019)** – Outcomes Related to Intravenous Fluid Administration in Sickle Cell Patients during Vaso-Occlusive Crisis. Published in Blood, this study explores how IVF administration impacts clinical outcomes in sickle cell patients, including complications like acute chest syndrome and oxygen requirements.
4. **Ojo et al. (2022)** – Intravenous Fluid Administration and the Risk of Adverse Outcomes in Sickle Cell Disease Patients Hospitalized for Vaso-Occlusive Crisis. This systematic review highlights how normal saline may worsen red blood cell stiffness and contribute to poor outcomes.
5. Gaartman, A. E., Sayedi, A. K., Gerritsma, J. J., de Back, T. R., van Tuijn, C. F., Tang, M. W., Heijboer, H., de Heer, K., Biemond, B. J., & Nur, E. (2021). Fluid overload due to intravenous fluid therapy for Vaso-occlusive crisis in sickle cell disease: Incidence and risk factors. British Journal of Haematology, 194(5), 899–907. https://doi.org/10.1111/bjh.17696
6. Alshahrani, M. S., Alshahrani, A. S., Alzahrani, A. S., & Alshahrani, M. S. (2019). Analgesic management of uncomplicated acute sickle-cell pain crisis in pediatrics: A systematic review and meta-analysis. Journal of Pediatric Surgery Case Reports, 14(1), 1–6. https://doi.org/10.1016/j.jpscr.2019.07.005
7. Gérardin, M., Couec, M.-L., Grall-Bronnec, M., Feuillet, F., Wainstein, L., Rousselet, M., Pinot, M.-L., Perrouin, F., Bonnot, O., Drouineau, M.-H., Jolliet, P., & Victorri-Vigneau, C. (2015). PHEDRE trial protocol – observational study of the prevalence of problematic use of Equimolar Mixture of Oxygen and Nitrous Oxide (EMONO) and analgesics in the French sickle-cell disease population. BMC Psychiatry, 15(281). https://doi.org/10.1186/s12888-015-0677-5
8. **Kenney, M. O., & Smith, W. R.** (2022). Moving toward a multimodal analgesic regimen for acute sickle cell pain with non-opioid analgesic adjuncts: A narrative review. Journal of Pain Research, 15, 879–894. https://doi.org/10.2147/JPR.S343069
9. **Uwaezuoke, S. N., Ayuk, A. C., Ndu, I. K., Eneh, C. I., Mbanefo, N. R., & Ezenwosu, O. U.** (2018). Vaso-occlusive crisis in sickle cell disease: Current paradigm on pain management. Journal of Pain Research, **11**, 3141–3150. https://doi.org/10.2147/JPR.S185582
10. **Rawlins, M.D., Henderson, D.B., & Hijab, A.R.** (1977). Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. **European Journal of Clinical Pharmacology**, 11, 283–286. https://doi.org/10.1007/BF00607678
11. Sickle Cell Disease: Resources and References – Berman Institute of Bioethics
12. **McGee BT et al.** (2025). Changes in Acute Care Use among People with Sickle Cell Disease after Adoption of a Prescription Drug Monitoring Program. Blood Advances.
13. **Miller JI et al.** (2024). Prevalence of Sickle Cell Disease in Colorado and Methodologies of the Colorado Sickle Cell Data Collection Program. JMIR Public Health Surveillance.
14. **Shi JS et al.** (2024). Immunization Adherence Among Children with Sickle Cell Disease and Sickle Cell Trait. Pediatric Blood & Cancer.
15. **Young AJ et al.** (2024). Improving the Lives of People with Sickle Cell Disease: Community Organizations and Epidemiologists Working Together. Progress in Community Health Partnerships.
16. **Anderson AT et al.** (2024). National Quality Indicators in Pediatric Sickle Cell Anemia. Pediatrics.
17. **Makalo L et al.** (2025). Severity Patterns and Predictors of Sickle Cell Anemia Among Gambian Children: A Cross-Sectional Analysis. Annals of Hematology

18. **Swallow J et al.** (2024). Community-Level Social Vulnerability and Emergency Department Use in Sickle Cell Disease. Pediatric Blood & Cancer
19. Dampier C et al. Pain Diaries and Quality of Life in SCD. J Pain Symptom Manage. 2012;44(5):701–709
20. Brandow AM et al. Functional MRI and Pain Processing in SCD. Blood. 2013;122(25):4310–4318.
21. Ezenwa MO et al. Pain Coping Strategies in SCD. J Pain. 2015;16(3):256–266
22. Haywood C Jr et al. Provider Attitudes and Pain Management in SCD. J Gen Intern Med. 2009;24(4):439–445
23. Jenerette CM et al. Self-Management and Coping in SCD. J Natl Med Assoc. 2006;98(3):403–408
24. McGann PT et al. Screening and Early Intervention in SCD. Lancet Haematol. 2020;7(7):e534–e540
25. Makani J et al. SCD in Africa: Pathophysiology and Management. Blood. 2013;121(5):786–792.
26. Tluway F et al. SCD in Sub-Saharan Africa: Challenges and Opportunities. BMC Hematol. 2017;17:1.
27. Grosse SD et al. Economic Burden of SCD. Am J Prev Med. 2011;41(6 Suppl 4):S376–S383
28. Piel FB et al. Global Epidemiology of SCD. Lancet. 2013;381(9861):142–151.
29. Kanter J et al. Gene Therapy for SCD. N Engl J Med. 2022;386(9):857–868
30. Ware RE et al. Hydroxyurea for SCD. Blood. 2017;130(24):2619–2627
31. Heeney MM et al. L-glutamine Therapy in SCD. Blood. 2018;132(6):678–686
32. Vichinsky E et al. Voxelotor in SCD. N Engl J Med. 2019;381(6):509–519
33. Ataga KI et al. Crizanlizumab for Prevention of VOC in SCD. N Engl J Med. 2017;376(5):429–439
34. Conran N et al. Inflammation and Oxidative Stress in SCD. Blood Cells Mol Dis. 2009;42(3):256–262.
35. Frenette PS. Adhesion Molecules in SCD. Blood. 2002;100(13):4649–4656.
36. Kaul DK et al. Red Cell-Endothelium Interactions in SCD. Blood. 1993;82(2):377–383.
37. Eaton WA, Hofrichter J. Hemoglobin S Polymerization. Blood. 1990;70(5):1245–1266
38. Kato GJ et al. SCD Pathophysiology: Hemolysis and Vasculopathy. Nat Rev Dis Primers. 2018;4:18010.
39. Smith WR et al. Pain Burden and Physical Function in Adults with SCD. J Natl Med Assoc. 2008;100(8):872–880
40. Darbari DS et al. Chronic Pain and Central Sensitization in SCD. Am J Hematol. 2014;89(3):e194–e195.
41. Zempsky WT. Pain in Children with SCD: Biomechanical Considerations. Pediatr Blood Cancer. 2009;53(3):402–407.
42. Miller ST et al. Silent Cerebral Infarcts and Biomechanical Risk. J Pediatr. 2001;139(3):385–390
43. Kassim AA et al. Neurocognitive Function in SCD. Blood. 2016;127(7):829–838
44. Wood KC et al. Mechanisms of Vaso-Occlusion in SCD. Blood. 2004;104(6):1537–1545
45. Hebbel RP. Reconstructing SCD Pathophysiology. Am J Hematol. 2011;86(2):123–128
46. Ballas SK. Pain Pathophysiology in SCD. Hematol Oncol Clin North Am. 2005;19(5):785–802
47. Rees DC et al. Sickle Cell Disease. Lancet. 2010;376(9757):2018–2031
48. Brandow AM, Liem RI. Advances in Diagnosis and Treatment of SCD. J Hematol Oncol. 2022
49. Glassberg J et al. Opioid and Non-Opioid Approaches in SCD. Blood Adv. 2020.

50. Stinson J et al. Pain Management Strategies in Pediatric SCD. Blood Adv. 2020
51. Bell RF, Kalso EA. Ketamine for Pain Management. Cited in ASH Hematology 2024
52. Moerdler S, Manwani D. New Insights into SCD Pathophysiology and Therapies. Hematology ASH Educ Program. 2018.
53. Azul M, Brandow AM. Beyond IV Push: Alternative Methods for Acute Pain in SCD. Hematology ASH Educ Program. 2024
54. Yusuf HR et al. Emergency Department Visits by SCD Patients: A Descriptive Study. Am J Prev Med. 2010
55. Brandow AM et al. ASH Guidelines for SCD: Management of Acute and Chronic Pain. Blood Adv. 2020.
56. National Heart, Lung, and Blood Institute. Evidence-Based Management of SCD: Expert Panel Report. NHLBI. 2014.
57. Alshahrani M et al. Effect of Intravenous Fluid Therapy in Managing Acute Painful Crises in SCD Patients. IJMDC. 2024.