International Journal of Research in Medical Sciences
Oza YR et al. Int J Res Med Sci. 2024 Aug;12(8):3079-3084
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20242249

Review Article

New horizons in sickle cell crisis treatment

Yugam R. Oza[1]*, Lovekumar Vala[2], Seelam R. S. Sai[3], Pradeep Valluri[3], Samudrala Rahul[3]

[1]Department of Medicine, Shri M P Shah Government Medical College, Jamnagar, Gujarat, India
[2]Department of Medicine, University of Northern Philippines, Philippines
[3]Department of Medicine, Santhiram Medical College, Andhra Pradesh, India

Received: 26 May2024
Revised: 01 July 2024
Accepted: 02 July 2024

***Correspondence:**
Dr. Yugam R. Oza,
E-mail: yugamoza7@@gmail.com

ABSTRACT

Even if life expectancy has increased, sickle cell disease (SCD) still presents difficulties, especially because of the painful episodes that occur frequently and without warning, known as Vaso-occlusive crises (VOCs). These crises are brought on by different cells adhering to one another and obstructing tiny blood veins, which can cause excruciating agony and eventually harm organs and tissues. While the majority of current treatments concentrate on symptom management and pain relief with the use of medications, hydration, and other general approaches, new discoveries about the fundamental mechanisms of VOCs provide intriguing new therapeutic options. With the goal of precisely addressing the pathways causing inflammation and cell adhesion, these cutting-edge treatments may lessen the frequency of VOCs and shield vital organs from harm. Though these treatments provide hope for improved SCD management, careful assessment and analysis of their efficacy and accessibility are necessary to guarantee their general benefit.

Keywords: Clinical manifestation, Novel therapy, Pathogenesis, Pain crisis, Sickle cell crisis, Sickle cell disease

INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder inherited in an autosomal recessive manner, stemming from mutations within the HBB gene, which codes for the beta-globin subunit of hemoglobin (HbA).[1] This genetic mutation entails the replacement of a glutamic acid codon (GAG) with a valine codon (GTG), causing a shift in the amino acid composition of hemoglobin from glutamic acid to valine. SCD causes anemia and occurrences termed "sickle cell crisis" (SCC). The prominent clinical characteristic of sickle cell disease is the "acute painful crisis," typically demanding hospital care. The phrase "sickle cell crisis" refers to a range of sudden medical conditions, such as vaso-occlusive crises (intense episodes of pain), aplastic crises, splenic sequestration crises, hyperhemolytic crises, hepatic crises, dactylitis, and acute chest syndrome. Other acute issues may include pneumonia, meningitis, sepsis, osteomyelitis, stroke, avascular necrosis, priapism, and venous thromboembolism.[2] Treatments for VOC have focused largely on the symptomatic management of the acute painful episode as opposed to prevention. However, to reduce the occurrence of these episodes and reduce the associated tissue and organ damage, specific treatments are required. In this review, we specifically discuss the current and emerging therapeutic options for sickle cell crisis in SCD.

PATHOGENESIS

The defining feature of sickle cell disease is a point mutation on the sixth amino acid of β-globin, which causes valine to substitute glutamic acid. In reaction to

oxygen deprivation, a mutant form of hemoglobin called hemoglobin S (HbS) polymerizes, giving erythrocytes a sickle shape and reducing membrane fluidity. Apart from erythrocyte sickling, a defining feature of sickle cell disease (SCD) is the persistent existence of basal inflammatory processes. Compared to individuals without the condition, SCD patients had greater baseline leukocyte counts. Soluble CD62L, a measure of neutrophil activation, is higher in SCD patients, despite the possibility that the overstimulated marrow from the underlying hemolytic process is responsible for the raised leukocytes. Moreover, greater activation molecules like CD64 and CD11b/CD18 are expressed by neutrophils in SCD. Monocytes with sickle cell disease (SCD) exhibit activated phenotypes and a greater inclination towards IL-1β and TNFα. The membrane of the erythrocyte gets damaged by HbS. Apart from the background polymerization that affects the membrane's fluidity, HbS precipitates on the inner surface after auto-oxidation and produces free radicals that are dependent on iron, which cause damage to the membrane. Although studies using intravital microscopy discovered that sickle erythrocytes are more likely to stick to leukocytes immobilized on endothelium than to endothelial cells directly, the broken membrane makes the erythrocytes more adherent to the endothelium. The damaged erythrocytes release free heme as a consequence of intravascular hemolysis. Complements are activated by free heme. By influencing macrophages through transcription factors including BTB and CNC homologue (BACH) 1 and Spi-C, it mediates pro-inflammatory activities. In the same direction, platelets in SCD have elevated levels of CD40L and are persistently active.[3] Activated platelets that release mitogenic mediators or vasoactive molecules promote in situ thrombosis4, all these factors resulting in Vaso occlusion and subsequent ischemia and infarction.

COMPLICATIONS

Following a Vaso-occlusive crisis (VOC) in hospital admissions, acute chest syndrome (ACS) is a major cause of mortality and morbidity in individuals with sickle cell disease (SCD). Children who take opioids are more likely to develop ACS, and even one ACS episode raises the risk in the future.[5] Acute cor pulmonale typically results from a pulmonary embolism or acute respiratory distress syndrome, but it can also occur from a vaso-occlusive crisis in a sickle cell anemia patient.6 Autosplenectomy, or recurrent splenic Vaso-occlusion, causes the organ to progressively atrophy and develop fibrosis. Over the course of the first five years of life, the spleen steadily loses size and function as a result of repeated auto infarction episodes and scarring. Children with sickle cell disease are more vulnerable to encapsulated bacterial infections when they have hyposplenism.[7] The spleen's white pulp is primarily composed of B cells arranged in T-cell periarteriolar sheaths and follicles. These B cells play a vital role in the generation of IgM antibodies that have the ability to opsonize bacteria that are encapsulated, including *Hemophilus influenza* type B, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Autosplenectomy makes the patients vulnerable to these infections.[8] In older children with sickle cell disease (SCD), transient aplastic crisis (TAC) caused by parvovirus B19 infection usually shows up as worsening anemia with reticulocytopenia and no splenomegaly.[9] Obstructive vasculopathy, a clinical manifestation of SCD kidney disease, affects arterial and capillary microcirculation, leading to abnormal vascular tone and activated endothelium. These abnormalities, particularly in the medulla and papilla in the kidney, can promote dysfunction and destruction through active endothelin (ET)-1 production, causing ischemia and sickling, and causing multiple ischemic hits during the vaso-occlusive crisis.[10] The acidic environment and hyperosmolality in kidney increase HbS concentration, leading to polymerization and impaired blood flow, resulting in ischemia, microinfarcts, and renal papillary necrosis.[11]

Patients with SCD typically involve the internal carotid artery and have cerebral artery stenosis and occlusion as a result of intima media proliferation. Angiogenesis pathways are then triggered, resulting in the formation of collateral arteries surrounding the Circle of Willis and the development of a non-inflammatory vasculopathy known as Moyamoya disease, which has a characteristic angiographic pattern. Hypoperfusion and hemorrhagic stroke predispose to recurrent ischemic strokes.[12]SCD disrupts intestinal microbiota balance and wall integrity, leading to bacterial translocation and inflammation. Vaso occlusive (VOCs) in the splanchnic vasculature compromises the intestinal barrier and mucosa's ability to host a normal microbiota. SCD patients are more vulnerable to bacterial inoculums and disrupt the normal intestinal microbiome.[13]

The cecum pathology in vaso occlusive crises shows mesenteric artery and arteriole thrombosis, hemorrhagic alterations, transmural necrosis, and acute inflammatory cell infiltration.[14] Sickle hepatopathy is used to describe all abnormalities resulting from the sickling process, including gallstone disease, hypoxic liver injury, hepatic sequestration, venous outflow obstruction, viral hepatitis (particularly in patients receiving multiple transfusions), hepatic crisis, and sickle cell intrahepatic cholestasis (SCIC). Recurring episodes might lead to chronic and progressive liver failure.[15]

Osteoarticular complications include Hand-foot syndrome (sickle cell dactylitis), osteomyelitis, infectious and inflammatory arthritis, stress fractures, bone infarctions, avascular necrosis and vertebral collapse.[16] Acute episodic pain crises known as "bone pain crisis" are brought on by sickle erythrocyte-induced microcirculatory blockage, which damages bone via ischemia-reperfusion injury and causes bone marrow necrosis.[17] Priapism is a significant complication of SCD. It can result in lifelong erectile dysfunction and is brought on by sickled erythrocytes impeding venous outflow.[18]

CLINICAL MANIFESTATIONS

Vaso occlusive crisis

Pain crises are a key symptom of sickle cell disease, resulting from blocked blood vessels causing tissue damage. Young children often experience painful swellings in their hands and feet, known as acute dactylitis or hand-foot syndrome. In adults, the pain usually occurs in the back, sternum, ribs, pelvis, or around the joints of long bones.[19] Chronic pain develops with patient age, due to nerve sensitization "Reports of ongoing pain on most days over the past 6 months, either in a single location or multiple locations" is one definition of chronic pain. Vaso-occlusive crisis (VOC) can be described in four phases. Phase 1-3 days with mild pain and numbness. Phase 2 sees a rapid increase in pain due to tissue damage from blockage. Phase 3 involves severe, constant pain and inflammation 3 to 5 days. Phase 4, resolution of the crisis 1 to 2 days. However, VOC can be unpredictable and not always follow this sequence, sometimes leading to a vicious cycle without resolution.[20]

Diagnosis of sickle cell disease

In sickle cell disease (SCD), red blood cells (RBCs) show various shapes and features like anisocytosis, poikilocytosis, polychromasia, nucleated RBCs, sickle-shaped cells, irregular contracted cells, and Howell-Jolly bodies (HJBs). Previous studies often only detected sickle-shaped RBCs when oxygen levels were lowered. However, we found that under normal oxygen levels, dense cells containing irreversibly sickled cells are more common.

NOVEL TREATMENT THERAPIES FOR SICKLE CELL CRISIS

Voxelotor

Sickle cell disease is defined by the clumping together of a type of hemoglobin called deoxygenated sickle hemoglobin (HbS). This leads to the creation of oddly shaped red blood cells that can clog blood vessels, causing painful crises throughout the body. These abnormally shaped red blood cells can't carry oxygen properly, which impairs blood flow to organs. Voxelotor, is a medication, that prevents the clumping together of hemoglobin S (HbS), a key factor in sickle cell disease. It belongs to a new class of drugs that alter the way hemoglobin carries oxygen in the blood. Voxelotor attaches to a specific part of the hemoglobin molecule, called the N-terminal valine of alpha chains, in a way that is both reversible and covalent.This therapeutic intervention represents a novel orally administered compound, characterized by its pioneering mechanism of action in enhancing hemoglobin's oxygen affinity, consequently mitigating the polymerization of HbS21. This medication also reduces the occurrence of events where red blood cells become sickle-shaped due to low oxygen levels in the blood, which in turn lowers the risk of complications such as hemolysis and blockages in blood vessels (vaso-occlusive infarction) in patients with sickle cell disease. During a phase I/II study, voxelotor exhibited a response in pharmacokinetics and pharmacodynamics that was dependent on dosage and was well received by both healthy volunteers and patients with Sickle Cell Disease (SCD). In a phase III trial (known as the HOPE trial), which was multi-center, randomized, and double-blind, a notably higher proportion of patients who were assigned voxelotor experienced an increase in hemoglobin levels (>1 g/dl from baseline) compared to those who received a placebo.

Anti-inflammatory agents

Anti-inflammatory medications play a crucial role in interrupting the series of events that lead to vaso-occlusion and VOC in SCD. Consequently, there is interest in drugs that target inflammation specific to SCD, as well as those with a broader anti-inflammatory scope. One such agent is Regadenoson, an adenosine A2A receptor agonist known to exert anti-inflammatory effects on invariant natural killer T (iNKT) cells, a subset of lymphocytes implicated in SCD's pathogenesis.[22]

In a phase II trial involving SCD patients hospitalized for a VOC, Regadenoson was administered to suppress iNKT cell activation. However, the trial did not yield a significant reduction in iNKT cells or impact the length of hospital stay, opioid use, or pain levels. Alternative strategies, such as higher doses or earlier administration, might have shown benefit, but long-term iNKT cell depletion using monoclonal antibodies could potentially be more effective in preventing VOC, although the role of iNKT cells in VOC pathogenesis remains uncertain. Another promising agent is NKTT120, a humanized monoclonal antibody demonstrating rapid and sustained deletion of iNKT cells in SCD patients without notable side effects. Unlike daily dosing, NKTT120 can be administered via infusion every three months. The next phase involves a randomized controlled clinical trial to assess its efficacy in reducing VOCs and the safety of prolonged iNKT cell depletion.[23]

Simvastatin

Simvastatin was linked to a substantial 85% decrease in the frequency of self-reported pain events, accompanied by a corresponding reduction in analgesic usage. However, despite this significant reduction in pain occurrence, there was no observed change in pain intensity with simvastatin treatment. In addition to the decline in pain rate, simvastatin treatment resulted in a reduction in several circulating inflammation mediators, including hs-CRP, sICAM-1, sICAM-3, sE-selectin, and sVEGF. These markers of inflammation and endothelial adhesion are typically elevated in SCD and other vascular disorders characterized by endothelial dysfunction,

indicating a state of sustained low-grade inflammation. The decrease in hs-CRP and other inflammatory markers following simvastatin treatment aligns with previous studies conducted in SCD patients and various multicenter studies involving non-SCD populations. Notably, in individuals with normal or low cholesterol but high hs-CRP levels, statins have been shown to significantly reduce the risk of stroke, disease progression, and mortality.[24]

Ticagrelor

Ticagrelor, an oral antiplatelet medication primarily used for acute coronary syndrome (ACS) or post-myocardial infarction (MI) treatment, has shown distinct properties that make it a promising candidate for sickle cell disease (SCD) management, despite other antiplatelet agents exhibiting inconclusive results in pre-clinical tests.[25] The pharmacokinetic characteristics of ticagrelor and its major metabolite meet the standard requirements for drug development, although factors such as gastrointestinal absorption, bioavailability, and metabolism can be influenced by the patient's clinical condition. Clinical trials, including phases I, II, and III, conducted under the 'the sickle cell program with ticagrelor (HESTIA)' have assessed ticagrelor's efficacy and safety in SCD patients and healthy volunteers from various countries. Phase I (HESTIA 4) focused on pharmacokinetics in pediatric SCD patients, showing rapid absorption and good tolerability. Phase II trials (HESTIA 1 and HESTIA 2) confirmed safety and tolerability while exploring efficacy. HESTIA 1 indicated a dose-dependent relationship between ticagrelor exposure and platelet aggregation inhibition in children with SCD, while HESTIA 2 did not find a significant effect on self-reported SCD-related pain attributable to ticagrelor. Currently, phase III trials under HESTIA3 aim to assess ticagrelor's efficacy and safety in preventing vaso-occlusive crises (VOC), with their outcomes being crucial in establishing ticagrelor's role as a therapeutic option for SCD management, either alone or in combination therapy protocols.[25]

Crizanlizumab

Despite advancements in understanding sickle cell disease's pathophysiology, treatment options for its complications, particularly sickle cell-related pain crises, remain limited. Hydroxyurea, the only FDA-approved drug shown to modify the disease's natural course, often fails to adequately manage symptoms, resulting in ongoing crises, organ damage, and reduced life expectancy. Moreover, adherence to hydroxyurea therapy poses challenges. Trials investigating new drugs for crisis prevention have generally yielded insignificant or clinically inconsequential results.[26]

In a randomized phase 2 trial, high-dose crizanlizumab treatment substantially reduced the annual rate of sickle cell-related pain crises by 45.3% compared to placebo, with significantly longer median times to the first and second crises observed in patients receiving high-dose crizanlizumab. These effects were consistent regardless of concurrent hydroxyurea treatment or sickle cell disease genotype. Among patients receiving hydroxyurea, the annual crisis rate was 32.1% lower with high-dose crizanlizumab, while among those not receiving hydroxyurea, it was 50.0% lower. Patients with various sickle cell disease genotypes were included, and high-dose crizanlizumab demonstrated lower crisis rates across different genotypes, suggesting its broad potential efficacy. Additionally, crizanlizumab treatment did not significantly affect markers of hemolysis, and its safety profile, with comparable rates of adverse events to placebo and no detectable antibody response, suggests its potential as a well-tolerated therapeutic option for sickle cell disease management. However, longer-term follow-up is warranted to monitor for potential late adverse effects.[26]

Gene therapy

In a major advance, the FDA on December 8th, 2023, approved a new gene therapy called Casgevy for treating sickle cell disease. Casgevy is the first-ever treatment to use CRISPR technology and is designed for patients twelve and older who experience recurring painful vaso-occlusive episodes.[27,28] Sickle cell disease is caused by abnormal adult hemoglobin (HbS) in red blood cells. Casgevy, a new gene therapy, aims to fix this by changing the type of hemoglobin produced. It does this by targeting a gene that normally suppresses the production of fetal hemoglobin (HbF), a type better suited for carrying oxygen. Casgevy uses CRISPR technology to edit this repressor gene in a patient's own blood stem cells, allowing them to produce more HbF. The treatment involves a two-step process. First, high-dose chemotherapy clears the patient's bone marrow. Then, the extracted stem cells are modified with Casgevy in a lab.

Finally, the edited stem cells are returned to the patient's body. The hope is that these modified cells will engraft in the bone marrow and start producing healthy red blood cells containing HbF. By increasing HbF production, Casgevy aims to reduce the sickling of red blood cells and alleviate the symptoms of sickle cell disease2728. In addition to Casgevy, the FDA also approved another gene therapy for sickle cell disease called Lyfgenia. Unlike Casgevy, Lyfgenia doesn't use CRISPR technology, instead it utilizes a lentiviral vector to achieve genetic modification of blood stem cells, with the goal of producing HbAT87Q, an analogue of HbA (normal adult hemoglobin). This approach aims to lower the risk of "sickling and occluding blood flow.[27,28] While the FDA approved Lyfgenia, there is a potential risk of blood cancer as a side effect. Because of this, Lyfgenia comes with a strong warning about this risk and the need for lifelong monitoring for any signs of cancer.[27,28]

Intravenous immunoglobulin

Researchers are studying intravenous immunoglobulin (IVIG) as a treatment for sickle cell disease. In animal studies, IVIG appeared to block a protein (Mac-1) on neutrophils that allows them to grab red blood cells. This also reduced how neutrophils stuck to blood vessel walls and interacted with red blood cells. A small patient study showed IVIG treatment reduced Mac-1 function. Currently, a larger clinical trial is underway to see if IVIG can shorten the duration of vaso-occlusive crisis (VOC), a painful complication of sickle cell disease.

CONCLUSION

Acute pain from vaso-occlusive crises (VOCs) is a primary reason individual with sickle cell disease (SCD) seek care. Current treatments like hydroxyurea, l-glutamine, and blood transfusions have limitations in fully addressing these painful episodes. Despite the global impact of SCD, well-designed, powerful trials to prevent VOCs are scarce. Promisingly, new therapies targeting the adhesion processes involved in VOCs are being investigated. These therapies, especially when combined with existing treatments, may reduce VOC frequency and related health complications while protecting endothelial cells and blood vessels, potentially preventing long-term organ damage. Managing acute pain during VOCs remains crucial, but concerns about opioid-related tolerance and dependency persist, and nonsteroidal medications pose risks like renal and gastrointestinal issues. Alternative non-opioid pain treatments exist, but their effectiveness is not well-established. New agents are being used for VOC treatment, and gene therapies show promise in potentially reversing or halting SCD progression by introducing wild-type hemoglobin. As these treatments progress, initiatives to ensure broader access to specialized care and treatments will be essential.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:204062072095500.
2. Hiran S. Multiorgan dysfunction syndrome in sickle cell disease. J Assoc Physicians. 2005;53:19–22.
3. Jang T. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events. J Trans Med. 2021;19:397.
4. Allali S, Maciel TT, Hermine O, Montalembert M. Innate immune cells, major protagonists of sickle cell disease pathophysiology. Haematologica. 2020; 105:273-83.
5. Yousef, A. Acute chest syndrome in pediatric sickle cell disease: A 19-year tertiary center experience. Ann Thorac Med. 2022;17:199.
6. Aubry A, Paternot A, Vieillard-Baron A. Cœur pulmonaire. Rev Mal Respir. 2020;37:257-66.
7. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol. 2014;166:165–176.
8. Brousse V. Acute splenic sequestration crisis in sickle cell disease: cohort study of 190 paediatric patients. Br J Haematol. 2012;156:643-8.
9. Yates AM, Hankins JS, Mortier NA, Aygun B, Ware RE. Simultaneous acute splenic sequestration and transient aplastic crisis in children with sickle cell disease. Pediatr Blood Cancer. 2009;53:479-81.
10. Tharaux PL. Endothelin in Renal Injury due to Sickle Cell Disease. 2011:185–199.
11. Bissonnette MLZ, Henriksen KJ, Delaney K, Stankus N Chang A. Medullary Microvascular Thrombosis and Injury in Sickle Hemoglobin C Disease. J Amr S Nephr. 2016;27:1300–1304 (2016).
12. Aggeli C. Stroke and presence of patent foramen ovale in sickle cell disease. J Thromb Thrombolysis. 2021;52:889-97.
13. Lim SH, Fast L, Morris A. Sickle cell vaso-occlusive crisis: it is a gut feeling. J Transl Med. 14, 334 (2016).
14. Gautam G, Harmon R, Foley R. Gastrointestinal vaso-occlusive crisis in sickle cell disease. Baylor University Medical Center Proceedings. 2022;35:856-7.
15. Praharaj, D. L. & Anand, A. C. Sickle Hepatopathy. J Clin Exp Hepatol. 2021;11:82-96.
16. Ferreira TFA. Chronic osteo-articular changes in patients with sickle cell disease. Advances in Rheumatology 61, 11 (2021).
17. Alagbe AE, Olaniyi JA, Aworanti OW. Adult sickle cell anaemia patients in bone pain crisis have elevated pro-inflammatory cytokines. Mediterr J Hematol Infect Dis. 2018;10:17.
18. Ahuja G. Priapism and sickle cell disease: special considerations in etiology, management, and prevention. Urol. 2021;156:40-7.
19. Vinnes EW, Lillemoen PK, Klingenberg O, Fjeld B, Iversen PO et al. Sickle cell disease – clinical manifestations and diagnostics.2023. Avialable at https://tidsskriftet.no/2023/02/kliniskoversikt/sigdcellesykdom-kliniske-manifestasjoner-og-diagnostikk.
20. Jang T. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events. J Transl Med. 2021;19:397.
21. Howard J, Hemmaway J, Telfer P, Porter J, Layton DM, Awogbade M et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood. 2019;133(17):1865-75.
22. Field JJ. Randomized phase 2 trial of regadenoson for treatment of acute vaso-occlusive crises in sickle cell disease. 2017;1:1645-9.

23. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:204062072095500.
24. Hoppe C. Simvastatin reduces vaso-occlusive pain in sickle cell anaemia: a pilot efficacy trial. Br J Haematol. 2017;177:620-9.
25. Ribeiro-Filho, J. et al. An evaluation of ticagrelor for the treatment of sickle cell anemia. Expert Rev Hematol. 202;13:1047-55.
26. Ataga KI. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. New. N Engl J Med. 2017;376:429-9.
27. Adashi EY, Gruppuso, PA, Cohen IG. CRISPR Therapy of Sickle Cell Disease: The Dawning of the Gene Editing Era. Am J Med. 2024;137(5):390-2.
28. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:2040620720955000.

Cite this article as: Oza YR, Vala L, Sai SRS Valluri P, Rahul S. Morphometric features of asterion in adult human skulls. Int J Res Med Sci 2024;12:3079-84.