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Total hip arthroplasty for sickle cell osteonecrosis: guidelines for perioperative management

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- The prognosis of sickle cell disease (SCD) has greatly improved in recent years, resulting in an increased number of patients reporting musculoskeletal complications such as osteonecrosis of the femoral head. Total hip arthroplasty (THA) can be utilized to alleviate the pain associated with this disease.
- Although it is well known that hip arthroplasty for avascular necrosis (AVN) in SCD may represent a challenge for the surgeon, complications are frequent, and no guidelines exist to prevent these complications. Because patients with SCD will frequently undergo THA, we thought it necessary to fulfil the need for guidance recommendations based on experience, evidence and agreement from the literature.
- For all these reasons this review proposes guidelines that provide clinicians with a document regarding management of patients with SCD in the period of time leading up to primary THA. The recommendations provide guidance that has been informed by the clinical expertise and experience of the authors and available literature.
- Although this is not a systematic review since some papers may have been published in languages other than English, our study population consisted of 5,868 patients, including 2,126 patients with SCD operated on for THA by the senior author in the same hospital during 40 years and 3,742 patients reported in the literature.

Keywords: hip osteonecrosis; sickle cell disease; total hip arthroplasty

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Introduction

Sickle cell autosomal recessive disease (SCD), is also known as sickle cell anaemia because of associated haemolytic anaemia, characterized by abnormally formed (sickle-shape) erythrocytes, which are destroyed and withdrawn from circulation leading to anaemia. Of greater clinical importance, sickle-shape cells cause vascular occlusion, resulting in ischaemia and tissue infarction. Patients homozygous for the sickle cell gene (SS haemoglobin) are at high risk of bone osteonecrosis[1] due to a microvascular occlusion related to a disturbance of red cell architecture and haemoglobin S polymerization. Reduced deformability in deoxygenated patients leads to an increased risk of coagulation in small vessels. The incidence of hip osteonecrosis is also high in those patients with haemoglobin SC (heterozygous compounds for Hb S and alleles producing Hb C, as result SC) and in different types of sickle cell beta-thalassemia (S/Thal) populations.[1]

Historically, SCD patients had a shorter life span[2] and died before the bone changes were clinically apparent. With modern diagnosis and therapy,[3,4] life expectancy has been increased and orthopaedic complications have therefore increased. This results in an increase in the rate of musculoskeletal conditions, such as osteonecrosis of the hip. Hip osteonecrosis occurs in approximately 50% of patients with SCD.[1–5] Some patients report that osteonecrosis results in a greater reduction in their life-quality[6] than the underlying cause. After hip collapse, pain and reduction of function may be severe, warranting surgery. Initial options include osteotomy or core decompression[7] with or without bone grafting but these are not always successful and therefore patients often require total hip arthroplasty (THA).

THA provides reliable symptomatic relief and improvement of function in osteoarthritis. However, postoperative outcomes and complication rates[8,9] in patients with SCD are less understood, due to reports in the literature[10] usually presenting a limited number of patients (less than 50 per article). There are several fundamental differences between SCD patients who have a multi-organ disease[2]

and the typical case (osteoarthritis) requiring THA, making the prediction of postoperative outcomes difficult in the first group based on knowledge of the latter. In this scenario, physicians need advice on perioperative treatment of THA in this population. This guideline only discusses the management of THA in adult patients with SCD. This guideline should be proposed for those who are considered suitable candidates for THA. We must caution against extrapolating this recommendation to other orthopaedic procedures such as TKA until additional data are available. This guide is intended for physicians, including rheumatologists, orthopaedic surgeons, and other physicians (haematologists) who perform perioperative risk assessment, as well as patients. The guideline addresses most of the common clinical situations, but may of course not apply to unusual situations. Open and informed communication is imperative between the patient, the orthopaedic surgeon and the haematologist. While cost in many countries is a very relevant factor in making healthcare decisions, it has not been included in this article, but this is one limitation of the recommendations.

Material and methods

The difficulty of the problem can be evaluated by consideration of the geography, epidemiology, and frequency of hip osteonecrosis related to SCD. There have been at least four mutational events occurring independently,[11] with three in Africa and a fourth in Saudi Arabia or central India. These events occurred from 3,000 to 6,000 generations ago, approximately between 70,000–150,000 years ago. The distribution of Hb S in the word is indicative of two factors: selection for carriers with survival advantages in malaria-endemic regions and subsequent migrations.

Although precise data are not available, a recent estimation[12] suggests that SCD concerns 0.74% of births in sub-Saharan Africa. By comparison, only 0.15 % of the black population of the United States and of Europe is affected by SCD. Sickle cell disease is also an important aetiology of hip osteonecrosis in the Indian subcontinent, in South America, in the Persian Gulf, in Mediterranean countries and those from the Caribbean, and Central America. It is estimated that each year over 300,000 babies (every decade 3 million) with severe forms of these diseases are born worldwide, the majority in low- and middle-income countries. Approximately 5% of the world's population are healthy carriers of a gene for sickle cell disease or thalassaemia. In high-income countries, the survival of people with SCD has increased steadily, often to adulthood. On the other hand, infant mortality related to SCD in Africa remains between 50% and 90%, with less than half of affected children reaching their fifth birthday. An index of the high mortality rate throughout childhood is the observation that the prevalence of Hb SS in adults is 10 times lower than the incidence of births (0.2–0.3% against 2–3%). Nearly 90% of the global population of people with SCD lives in three countries: India, Nigeria, and the Democratic Republic of Congo, where 2% of the population is affected by the disease and the prevalence rate of carriers (trait sickle cell) reaches 10–30%. According to these data and to some extrapolations, SCD affects several million adults worldwide. Specific orthopaedic manifestations of SCD and its sequelae include osteonecrosis, infection, and bone marrow hyperplasia. Osteonecrosis of the femoral head (ONFH) has been reported in up to 50% of SCD patients based on the type of haemoglobinopathy.[1–4] With this frequency (50%) and the presence of bilateral osteonecrosis most often in this population, the number of people with hip osteonecrosis due to SCD is probably several million in the whole world but only a small number of patients will have access to THA.

Methodology, experience, literature and data analyses

This guideline uses Grading of Recommendations Assessment, Development and Evaluation (or GRADE methodology) to rate qualities of available evidence and to develop recommendations.[13] Using GRADE, recommendations can be either strong or conditional,[13–14] depending on the authors' experience and the evidence in the literature.

Our experience is based on around 60 SCD THA each year for more than 40 years in the same hospital, with as a result more than 2,000 THAs in this disease, with some results reported in the literature.[15] Due to the presence of a national reference centre for this disease, the medical status of patients and prevention of complications were monitored by a medical team experienced in the preoperative management of patients undergoing orthopaedic procedures. Our study population consisted of 2,432 hips operated on for THA in 2,126 patients with SCD by the senior author in the same hospital (Henri Mondor Hospital, University Paris East).

To confirm or nuance our experience we selected papers from four databases: Medline, Embase, PubMed, and Cochrane Library during June 2019. The following search algorithm was used: ((“Sickle cell disease” or “SCD”) AND (“total hip arthroplasty” or “total hip replacement*” or “hip replacement*” or “hip arthroplasty” or “THA”)). No limit was set for date of publication but only English-language articles were included. Data were analysed and synthesized from eligible studies. When available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the number of participants, and the absolute effects. The quality of evidence for each critical and important outcome was rated as very low quality, low quality, moderate quality, and high quality, evaluating limitations of the study design.

Duplicates were removed and the abstracts of all the articles were reviewed. The data were obtained from the selected studies[6,9,15–29] and included: preoperative and postoperative management, sample size, patient characteristics, implant type (i.e. cemented or uncemented), morbidity, mortality, length of follow-up, hip scores, medical and surgical complications. Although this is not a systematic review since some papers may have been published in languages other than English, our study population consisted of 5,868 patients, mixing 2,126 patients with SCD operated on for THA by the senior author in the Henri Mondor Hospital and 3,742 patients reported in the literature.

Moving from evidence to recommendations

This article discusses the evidence in the context of both the clinical experience of the senior author and the input from the literature. An 80% agreement defined the threshold for a strong recommendation, with 40% of points for experience of the authors and 60% for the literature. This means, for example, that for the risk of infection the authors agree with this risk and 80% of the papers found an increased risk, arriving at 88%, with as a result a strong recommendation to prevent this risk. If 80% agreement was not achieved during analysis this consideration led to rating down the quality of evidence (conditional recommendation) due to indirectness of results, heterogeneity in samples particularly and imprecision associated with small sample sizes; for example, the choice of the implant type (cemented, uncemented, polyethylene, ceramic, dual mobility) usually did not reach more than 40% agreement.

How to interpret the recommendations

Much of the evidence was indirect, coming from medical or surgical studies. A strong recommendation indicates that most or almost all informed patients would choose the recommended action. Conditional recommendations are those in which the majority of the informed patients would choose to follow the recommended course of action, but a minority might not.[30–31]

In a guideline, recommendations are strong or conditional in relation to the level of the evidence. A conditional recommendation means that the positive effects of following the recommendation will probably outweigh undesirable effects; so, the recommendation could apply to the majority of patients, but might not apply to all patients. Therefore, a conditional recommendation always warrants a shared decision-making approach. The most important limits of these recommendations are due to the fact that articles from the literature come from America, Europe, and the Middle-East, while nearly 90% of the world's SCD population lives in three countries: Nigeria, India, and the Democratic Republic of Congo; and the English-language literature does not give many data about THA in these countries.[22]

Results (recommendations and guidelines)

Precise diagnosis of the disease before THA is a strong recommendation

In populations of African ethnic origin, a patient with hip osteonecrosis should be screened for SCD. Diagnosis of sickle cell disease is based on analysis of haemoglobin. This analysis involves chromatography or protein electrophoresis, which are cheap techniques and available worldwide.

Sickle cell trait (the heterozygous Hb SA) with one abnormal sickle gene designated S and one normal haemoglobin gene designated A, is a benign condition[32] from an orthopaedic point of view; however, it is associated with an increased risk of a rare renal tumour, medullary carcinoma. Patients with sickle cell trait have no propensity for vaso-occlusive complications, no risk of osteomyelitis, and no particular risk for osteonecrosis; when osteonecrosis is observed, another cause should be researched.

The term sickle cell disease[11,12] refers to all the genotypes that cause the characteristic clinical syndrome whereas sickle cell anaemia, the most common form of sickle cell disease, refers specifically to homozygosity for the βS allele. In populations of African ethnic origin, sickle cell anaemia typically accounts for 70% of cases of sickle cell disease, with most of the remainder having haemoglobin SC disease (Hb SC disease) owing to the coinheritance of the βS and βC alleles. The third major type of sickle cell disease occurs when βS is inherited with a β-thalassemia allele, causing Hb S/β-thalassemia.

Overall, Hb SS accounts for 60–70% of cases of sickle cell disease[11–12] and has the severest clinical manifestations of any of the sickle cell disease variants, with the higher risk of morbidity and mortality (if the diagnosis is unknown) during or immediately after THA.[8,9,33]

Preoperative transfusion status evaluation is a strong recommendation

Part of the routine evaluation of patients with sickle cell disease should include laboratory tests consisting of serial haemoglobin Hb S%, renal function, liver function, and oxygen saturation. Based on these laboratory tests, the need for preoperative transfusion can be determined. There is a general trend toward a conservative rather than aggressive transfusion regimen.[34–35] By adopting a simple transfusion therapy, transfusion-related complications in patients are decreased. Red blood cell exchange to decrease the haemoglobin S level to less than 30% is only performed preoperatively in patients with a history of severe acute chest syndrome,[35] a previous cerebrovascular episode, or severe anaemia with haemoglobin less than 5 g/dL.

Around 100% of patients operated on with primary THA will need transfusion during or after surgery. The most immediate complication is blood loss requiring several transfusions and resulting in transfusion reactions. Given the frequency of antigen mismatch between mostly Caucasian donors and African-origin recipients and in an attempt to prevent alloimmunization, blood products which are phenotypically typed for ABO, Rhesus (Cc, D, Ee), and Kell should be selected. All patients should have antibody screening before surgery.[15] It is necessary to verify that blood products are available for the patient before beginning the surgery. Sometimes the donor registry for an entire country may be used as a resource when necessary.

This population with SCD has an increased blood loss during THA as compared with blood loss for the same surgery in patients without the disease. There are several causes for this abnormal blood loss: (1) the procedure may be technically more difficult in patients with SCD, due to abnormal anatomy such as acetabular protrusion, or due to difficulties in preparing the femoral canal; (2) also, blood loss increases in patients who have preoperative transfusions, have developed alloantibodies, or need red blood cell exchange; this phenomenon has been reported by Vichinsky et al,[8,34] in patients with THA. The replacement of blood products in this population with preoperative anaemia decreases cardiopulmonary complications. The goal is to keep postoperative haemoglobin higher than 8 mg/dL in patients with SCD with a target of 10 mg/dL. However, due to multiple transfusions, alloimmunization is frequently seen in this population with the risk of major transfusion reactions and impossibility to obtain the target of 10 mg/dL.

Prevention of infection is a strong recommendation

Studies have reported higher risk of postoperative wound infections in THAs related to SCD as compared with other causes of THA. The defective activation of complement's pathway is facilitated by a non-functioning or absent spleen. This increases the risk of infection by encapsulated bacteria.[8] Therefore, there is a weakened immune response in patients with SCD that may account for an increased risk of infections such as pneumonia, bone sepsis, wound infection among these patients. It has been suggested that this might be the cause of the higher prosthetic joint infection rate compared to other patients with osteonecrosis.[9]

Identification of sources of infection is a strong recommendation

Chronic stasis ulcers in patients with SCD are just one of many potential sources of infection and should be treated. All patients with gallbladder stones should have their gallbladder removed before hip surgery because gallbladder infection is a major source of secondary bone infection, due to micro-infarcts present in the gallbladder. Surgery should be performed only when white blood cell count, erythrocyte sedimentation rate, and C-reactive protein values are within normal limits (according to the disease). Patients with sickle cell disease tend to contain latent *Staphylococcus* and *Salmonella* organisms in the infarcted bone due to the frequency of osteomyelitis in childhood.[36] To identify latent infection and determine appropriate antibiotic therapy, culture of the femoral head bone chips and histology of all surgical specimens should be obtained during THA.

Antibiotics (first- and second-generation cephalosporins; 2.5 g per day) should be administrated during and after surgery (three days). Furthermore, all patients should have their implants fixed with cement containing antibiotics when the choice is a cemented implant. After the operation, the antibiotics are continued for three days if intraoperative cultures were negative and for one month if the cultures or histological examination were positive. No empirical coverage of *Salmonella* is generally necessary.

Vitamin D supplementation is a conditional recommendation to decrease infection

Could an infection prevention be as simple as vitamin D supplementation? Vitamin D is one of the most ancient molecules[37] known for calcium regulation,[38] but also more recently for macrophage activity.[39] There is no direct evidence of vitamin D efficiency to decrease THA infection in SCD, but there is a possibility that it could be efficient at a low cost. Vitamin D deficiency is now recognized as one of the most common nutritional conditions among persons with SCD[37–39] and there are characteristics specific to SCD that may contribute to this phenomenon.[40] First, decreased synthesis of vitamin D in the skin due to increased melanin. Second, it has been reported that 80% of African Americans have some degree of lactose intolerance and therefore may avoid vitamin D rich foods, which suggests that those with SCD may not be meeting these increased nutritional demands. Maier et al[41] demonstrated that there was a significant decrease in serum vitamin D levels of patients with hip arthroplasty without infection and those with infection. This recent report highlights the potential role of vitamin D in the prevention of infection, phenomenon confirmed by Hegde et al[42] in an animal model of joint infection. Therefore, since vitamin D is relatively harmless, vitamin D supplementation could be distinctly low risk and high reward in patients with SCD.

Withholding new biological agents (Hydroxyurea) prior to surgery is a conditional recommendation

Many patients with SCD have Hydroxyurea treatment. Hydroxyurea is a simple chemical compound synthesized in 1869. A century later, Hydroxyurea was first introduced

as a clinical agent, primarily as chemotherapy to treat various solid tumours and leukaemias.[43] Due to early efficacy as an antineoplastic agent, Hydroxyurea was first approved by the US Food and Drug Administration (FDA) in 1967. In the mid-1980s, Hydroxyurea was shown in proof-of-principle studies to induce Hb F in sickle cell anaemia (SCA),[43,44] and Hydroxyurea received FDA approval for the treatment of adults with severe SCA in 1998.[44] The most commonly encountered short-term toxicity includes mild and reversible cytopenia, which is an expected result, but may be an inconvenience before orthopaedic surgery, particularly as regards granulocytes. Because of the predicted myelosuppression, patients undergoing Hydroxyurea treatment require complete blood counts before surgery. If any toxicity criteria are present, Hydroxyurea should be temporarily suspended for one week, to allow blood count recovery.

During preoperative management, CT scan and MRI are conditional recommendations

Deformities of the hip in adults who have sickle cell disease are frequently due to possible previous avascular necrosis in childhood.[45] Therefore, a detailed patient history, physical examination, and radiographic evaluation are required for SCD patients undergoing primary THA. The history of patients should focus on prior treatments, surgeries, and complications. The patients' conditions (leg length, fatigue, limp) and pain patterns should be thoroughly discussed. Physical examination of these patients often reveals abnormalities in size, range of motion (stiffness or laxity), leg lengths, and prior incisions, which can cause difficulty in surgery. Surgeries of the contralateral limb, such as epiphysiodesis, should be noted. Thorough preoperative assessment of femoral and sciatic nerve function is essential due to the high rate of complications in these patients.

Plain radiographs should include anteroposterior radiographs of the pelvis and lateral radiographs of the involved hip. When abnormalities due to abnormal growth are detected, computed tomography (CT) scans may be indicated to provide accurate assessment of anteversion, femoral canal dimensions, and acetabular bone stock assessment. Due to frequent bilaterality of the disease,[1–5] magnetic resonance imaging (MRI) should be performed on the contralateral hip if pain is present and radiographs are normal. Contralateral cell therapy[46,47] at the early stage may be performed during the same anaesthetic in these patients.

Evaluation of technical difficulties before surgery is a strong recommendation

The femoral canal is frequently sclerotic, needing intramedullary reaming in 70% of cases.[25] Preparation of the proximal femur may need a combination of incrementally sized reamers. In some situations, the medullary canal is very thin or the femur appears as a thin cortical lining inside the true cortex which makes it impossible to use rasps. It may be necessary to use reamers or to perform a femoral cortical window to avoid intraoperative perforation of the femoral shaft. In some situations, a short stem could be considered.

Historically, rasping the femur during cemented hip arthroplasty was developed to properly size the femoral canal and create an adequate cement mantle. Normally, rasping the endosteal canal provided the surgeon with the tactile sensation to reliably size the femoral canal and ensure an adequate cement mantle. This may be very difficult to obtain in SCD, and particularly the tactile sensation is different during reaming. After reaming, the endosteal canal has become round. According to senior experience, after reaming it is better to use the larger stem to obtain partial contact of the stem on the bone to block the risk of rotation (usually prevented by a non-rounded shape rasp), the cement being just a filler of the space. Trying to keep a thick mantle of cement after reaming increases the risk of rotation between the cement mantle and the round-shaped endosteal canal.

Femoral canal preparation in cementless total hip arthroplasty requires rasping the proximal femur to create an osseous envelope for component implantation. However, since the femoral canal is frequently sclerotic the concept of 'fit and fill' that was coined to address an ingrowth stem fit into the proximal femur with contact area to host bone may be difficult to obtain, and the usual tactile sensation and perception of change of sound during rasping is also more difficult to obtain. When reaming is necessary to prepare the femur, the authors recommend the use of a cemented stem, since the contact will be difficult to obtain between a round endosteal canal and the shape of the femoral stem.

The rate of femoral perforation appears high in sickle cell disease. Rates of shaft perforation and per-operative fractures range from 2% to 15% in the literature.[25] Therefore, some authors have recommended a window[25] to prepare the femur and avoid this risk with cementless implants. Fracture occurred historically most commonly during insertion of trial or final components, but may become apparent in the first year. Cemented implants are not without significant fracture risk, particularly if cement extravasation occurs through an unrecognized intraoperative perforation. Due to these risks, the surgeon needs to verify before surgery that reamers, cerclage wires or Parham bands, plate and screws and bone grafting are possible, as well as longer stem implants, and revision prostheses. Due to this risk of difficulties with the femur, the choice of the approach (anterior, lateral, or posterior)

should be discussed according to anatomical difficulties and the experience of the surgeon.

Heterotopic ossification[9] is frequently observed. This is in relationship to the high number of mesenchymal stem cells in the bone marrow of these patients, and the absence of prevention of ossification using non-steroidal anti-inflammatory drugs to avoid an increased risk of haematoma in this population. Cemented stems appear to decrease the risk of ossification in the personal experience of the senior author.

Patients with SCD have increased risk of wound complications;[8] this includes wound drainage and haematoma formation. Nerve injuries have been described and are related to haematomata.[8] Therefore, drainage is a strong recommendation for these patients.

Choice of specific implants is a conditional recommendation

Uncemented or cemented implants

Given the young age at which SCD patients may undergo total hip replacement, greater demands are placed on the arthroplasty. SCD patients are at higher risk of requiring revision and repeat surgery long term as compared to other populations. Using cement with antibiotics may reduce the risk of infection, and cemented hips might produce more favourable results in patients with a poor bone quality that may jeopardize the quality of bone integration achievable by uncemented implants in bone that may be largely necrotic. There are some other advantages of cemented fixation, including additional haemostasis and decreased risk of femoral perforation. However, there are no real comparisons between cemented and uncemented hip to adequately assess this, and there might be some advantages in the presence of cardiac disease to using uncemented THA in this population to avoid complications of cementing.

Bearing surfaces

Recently, the THA bearing surface has been identified as a potential predictor of joint infection which could be an important factor in SCD. More specifically, some published studies[48] have found a higher risk of infection with metal-on-polyethylene (MoP) THA than ceramic-on-ceramic (CoC) bearings. We checked which bearing surfaces, and infection rate in SCD patients[49] who had bilateral THA with different bearings performed in our hospital by the same surgical team from the year 1981 to the year 2010 (mean follow-up 15 years; range 7 to 35 years). We evaluated 325 patients (650 hips) with sickle cell disease (SCD) with two different bearings on each side. In sickle cell disease, MoP hips had higher risk of infection (26 out of 219) when compared with CoP (9 out of 222; $p = 0.002$), and CoC (1 out of 209 hips; $p = 0.0004$); with increase over time from 1% at one year to 4% with CoP, and from 1% to 11.8% with MoP. Ceramic-on-ceramic bearings with cemented stems revealed another advantage in these young patients: when the contralateral hip of the same patient was the control, after 40 years of follow-up, postoperative fractures occurred 30 times less on the side with a CoC bearing compared with the side with a polyethylene cup.[50] Ceramic-on-ceramic also decreases wear and osteolysis, and therefore should be implanted when possible.[51]

Prevention of dislocation

Hip dislocation is also a complication reported in patients with sickle cell haemoglobinopathy. This may be due to changes in the anatomy seen in these patients with SCD[45] or to frequent haematomata. Rates of dislocation vary in this population and also are increased in obese patients. Sickle cell disease has historically been associated with poor nutritional status rather than obesity. However, some patients have many general risk factors and disease-specific characteristics, such as ethnic distribution and sedentary lifestyle, that may increase their risk for obesity.[52] In contrast to traditional thinking, 15% of SCD patients in our practice were overweight and obese. Obesity is more common in patients with less severe disease and in older adults. Additionally, obesity is associated with increased risk of SCD-related morbidities such as hypertension and is associated with more hospitalizations. For these obese patients and particularly when anatomical abnormalities are present, we used dual mobility implants[53] to prevent dislocation.

Postoperative recommendations for transfusion, hydration, oxygen, opioids

Transfusion

A frequent complication is immediate blood loss requiring transfusions and sometimes resulting in transfusion reactions. Congestive heart failure may occur in some patients; chronic anaemia requires attention to fluid balance and management by a haematologist familiar with sickle cell patients. Transfusion complications may be decreased with a conservative transfusion approach. The goal is to keep postoperative haemoglobin around 10 mg/dL in these patients,[8] who have preoperative anaemia, to decrease cardiopulmonary complications.

Acute chest syndrome is rare, but as a form of acute lung disease can be a cause of mortality in sickle cell patients.[8] The diagnosis of acute chest syndrome is clinical with the presence of pulmonary infiltrate on a chest radiograph, with respiratory symptoms, hypoxaemia, and fever. Intubation may be necessary when symptoms progress. Due to a high risk of mortality, aggressive treatment includes oxygenation, antibiotics as needed, and exchange

transfusions.[8] Acute chest syndrome is also characterized by a combination of respiratory symptoms, with pain in the thorax or abdomen. This syndrome is often recurrent and affects 20% of those with SCD.[8] Although there is great variability in outcome, acute mortality rate is as high as 5%. Furthermore, acute chest syndrome is a major risk factor for patients with chronic lung disease. The aetiology of this syndrome is a complex interplay of venous pulmonary embolism and/or fat embolism, infection, and in situ microvascular plugging by sickled red cells. Consequently, many advocate exchange transfusions before surgery for patients with acute chest syndrome, and our experience with postoperative acute chest syndrome supports this recommendation.

Hydration and oxygen

Other immediate complications may include vaso-occlusive crises. It is imperative to prevent crises through appropriate fluid maintenance and adequate oxygenation. Vaso-occlusive crises present as pain and are managed with parenteral fluid administration and analgesics. Intracellular dehydration is a known trigger for Hb S polymerization. Whenever possible, prolonged preoperative fasting must be avoided. Patients should be encouraged to drink clear fluids up until six hours before surgery. For patients undergoing moderate or major procedures such as THA, intravenous hydration must be used before surgery. Normal saline (9 g/dl of sodium chloride contains 154 milliequivalents of sodium, has a pH of 5.5, and osmolarity of 308 milliosmoles per litre) is acidic and increases the viscosity of blood;[54] hypotonic fluids, in theory, decrease sickling and are preferred.[55] Excessive fluid loading is associated with pulmonary oedema and can precipitate acute chest syndrome and thus needs to be avoided. Hypoxia is the most important trigger of sickle cell crisis and also needs to be avoided. Routine use of oxygen supplementation is necessary during the first two postoperative days. Oxygen monitoring in the perioperative period must be considered mandatory in all patients. However, pulse oximetry does not correlate well with arterial oxygen tension in some SCD patients. It is therefore important that arterial blood gas confirmation is obtained in hypoxic patients.

Pain management

Treatment of pain in sickle cell disease is one of the most daunting tasks of the disease's management. It requires a comprehensive team strategy.[56] The most common form of pain occurs during vaso-occlusive episodes, which may arrive in the postoperative period. Acute pain, which is not treatable at home, requires parenteral opioids and hydration; as a consequence, for THA, the SCD patient needs at least three days of hospitalization. Optimal analgesia usually requires opiates given at time intervals or administrated by a patient-controlled analgesia device. Non-steroidal anti-inflammatories are usually avoided due to an increased risk of haematomata with these analgesics. Patient-controlled analgesia (PCA) is reported to be as safe and effective as intermittent opioid injections, and usually consists of diamorphine subcutaneous infusions. PCA is used for patients who prefer it to intermittent injections. If pain is not controlled, the amount of opioid is increased in small increments (e.g. diamorphine 2–3 mg) to avoid the risk of central nervous system depression. When the acute pain begins to resolve, the dose is tailed off gradually rather than stopped abruptly, so as to avoid withdrawal symptoms, which can mimic those of sickle cell crisis. These strategies apply to intermittent injections or oral administration of opioids, not to PCA when opioids are used as part of pain management in SCD, and their side-effects must be prevented or treated. Many patients develop pruritus when given morphine, and this commonly responds to oral hydroxyzine 25 mg twice daily. Pruritus does not imply allergy to morphine and does not warrant stopping the drug or switching to pethidine. A transition to oral opioids should be considered for postoperative pain control once the patient is tolerating oral intake and is able to ambulate.

Thromboembolic prophylaxis is a strong recommendation; medication is a conditional choice

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), has recently been recognized as a common complication of sickle cell disease. One study has reported that the overall prevalence of pulmonary embolism was four times higher in SCD patients as compared to the African American population without SCD.[57] Another study of patients hospitalized in Pennsylvania has reported a frequency of pulmonary embolism 50-fold greater in the SCD population as compared with the general population.[58] The incidence of venous thrombosis is, cumulatively, 11.3% at the age of 40 years.

Prevention with anticoagulation

Patients with SCD need prophylactic anticoagulation for one month after surgery. Three types of anticoagulation have been tested.[59] Warfarin and acenocoumarin reduce the markers of coagulation activation but have no effect on the frequency of painful episodes. Low molecular weight heparin (HPBM) decreases the severity of painful crises and, as a consequence, the duration of hospital stay. The frequency of haematomata is lower with HPBM than with warfarin. With HPBM the problem is the risk of thrombocytopenia when the patient is being treated with Hydroxyurea, or due to splenic sequestration. Although it

occurs very rarely in adulthood, splenomegaly may be present and induce thrombopaenic hypersplenism. A recent study evaluated the efficiency of 'factor Xa inhibitor rivaroxaban' on VTE and concluded that this Xa inhibitor is not non-inferior compared with warfarin in SCD.[60] Adult sickle cell patients are prone to develop haemorrhagic stroke. For this reason, standard anticoagulant therapy and doses may not be optimal. In addition, the provider's assessment of the patient's ability to adhere to medical instruction and safely take the medications as prescribed is important.

Diagnosis of thrombophlebitis

Symptoms of VTE have the risk of overlapping with other complications in sickle cell disease.[61] Bilateral oedema might be attributed by mistake to a right heart failure, or to a kidney or liver disease, but when oedema has unequal distribution this may indicate VTE. When unilateral and painful, oedema might be attributed by error to cellulitis, complication of leg ulcers, or bony infarct. Short breath, pleurisy, and hypoxaemia are often attributed to pneumonia. Pulmonary embolism also may be the cause of wheezing and infiltrates. Therefore, a high clinical suspicion for thrombophlebitis is recommended in SCD, and diagnostic evaluation with Doppler should be carried out with a low threshold according to the fact that D-dimer level[62] is often elevated in SCD and, unlike the general population, is not helpful for VTE diagnosis. Interpretation of ultrasound Doppler does not appear to be different for patients with SCD.

Computerized tomographic pulmonary angiography (CTPA) is widely used to detect pulmonary embolism. However, abnormalities may be confused in patients with acute chest syndrome (ACS) due to a high prevalence of pulmonary thrombosis.[62] Even in the absence of ACS, the possibility exists that small defects on CTPA may represent sickling rather than a classical clot. Radionuclide scanning (V/Q scan) offers some advantages for the diagnosis of pulmonary embolism by minimizing radiation exposure, and has well-defined diagnostic criteria.

Treatment of thrombophlebitis

Despite prophylaxis, thrombophlebitis is possible. The choice of anticoagulant to treat venous thrombosis in SCD has not been well investigated. The focus of previous studies was generally on prevention. Recently, safety and effectiveness have been studied.[63–64] At 15 days, warfarin was not in the therapeutic range for many patients and the majority of these patients reported non-adherence to treatment. Venous thrombosis recurrence was therefore frequent (25% at 90 days).

Another study also reported recurrence with HPBM, and Rivaroxaban after the initial VTE event in SCD.[65] The high risk of recurrent thrombophlebitis in patients with SCD raises the question of whether these patients should be considered for a longer period of anticoagulation. As many patients with SCD seem to have poor adherence to treatment, and may also have liver or renal dysfunction that increase the risk of bleeding, intermittent re-assessment of benefit versus risk of anticoagulation is necessary.

Conclusions

The recommendations that form this guideline are not exactly treatment mandates, but can be used to promote valuable discussion regarding management prior to, during and after surgery. The authors recognize that probably not all potential clinical scenarios are covered by the guideline, but the most common clinical situations are addressed. This guideline cannot not replace clinical assessment and optimization, and also it remains very important to discuss the risks and benefits of this surgery as patients and physicians are preparing for THA.

The prognosis of patients with SCD has improved in recent times, and life expectancy has considerably increased. Therefore, improving quality of life by managing musculoskeletal complications (especially osteonecrosis of the hip) is of great value to these patients. In patients with collapse and persistent pain, THA is the only option for pain relief and functional improvement. However, postoperative complications are frequent in patients with SCD. THA in sickle cell disease (SCD) is associated with increased duration of stay and hospital charges[9] even in hospitals with experience of these patients. This review therefore examined the literature concerning hip replacement surgery in patients with SCD. Before and after THA, patients with SCD should be closely monitored for these adverse events. There is a wide range of reported postoperative mortality rates (less than one month) in the literature, ranging from 1% to 5%. This is high considering that the average age of surgery is around 35 years old. A large number of death reports were published in the 1990s, but this risk persists in recent reports,[9] and often surgeons do not realize this risk frequency, particularly when they perform only on a small number of patients. Absence of diagnosis of the disease, haemodynamic deficiency due to anaemia and infection are the leading causes of mortality and morbidity in patients with SCD. Assessment of oxygenation and haemodynamic status minimizes complications associated with sickle cell disease in patients undergoing surgery.

Given the young age at which SCD patients do develop osteonecrosis, in the early stages of osteonecrosis, basic decompression with or without cell therapy[65,66] is an option to prevent progression of the disease and to avoid

the risk of THA. Patients should be informed of this possibility to allow early diagnosis and treatment when hip pain is detected.

When THA is necessary, SCD patients are at higher risk of requiring revision and repeat surgery in the long term as compared with other populations. Good numbers of studies of THA in this disease have been published recently with good results. Azam and Sadat-Ali[6] reported on 87 uncemented THAs with a survival rate of 92.6% at 7.5 years. Ilyas et al[26] have studied the long-term results of 133 uncemented hips with a mean follow-up of 14.6 years and a 94.1% survival rate at 15 years. With a mean follow-up of 13 years, one of the largest series reported on THA in SCD by Hernigou et al[15] has a 10-year survival rate of 89% in 312 THAs in 244 patients. Progress in the fixation of the implants may occur in the future.[67] However, one should remember that these series are performed in countries with experimented teams, and that there exists heterogeneity in series reporting results of THA in SCD patients. What may appear as a long term (10 years) in the literature at present remains a relatively short term when THA is performed at 25 years of age with regard to the current life expectancy of these patients.

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